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Arnold, L.A.; Naasz, R.; Minnaard, A.J.; Feringa, B.L.

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Catalytic Enantioselective Synthesis of (-) Prostaglandin E_1 Methyl Ester Based on a Tandem 1,4-Addition-Aldol Reaction

Leggy A. Arnold, Robert Naasz, Adriaan J. Minnaard and Ben L. Feringa*

Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
feringa@chem.rug.nl

Supporting information

Contents:

General procedure for the acetalization of 2-cyclopenten-1,3-dione (7a-7e). To a cooled solution (0°C) of cyclopenten-3,5-dione (1.92 g, 20 mmol) and BF_3*Et_2O (2.52 ml, 20 mmol) in chloroform (50 ml) was added the alcohol (40 mmol, 20 mmol for diol). After stirring for 3 h the reaction mixture was poured into NH_4Cl (aq) and extracted three times with 25 ml diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (SiO_2 ether/pentane) gave the corresponding acetals.

4,4-Dimethoxy-2-cyclopenten-1-one (7a). Purification by column chromatography (SiO_2 hexane/diethyl ether, 1:3, Rf = 0.37) gave 710 mg (26%) of **7a** as a colorless liquid. ^{1}H-NMR (300 MHz) δ = 7.52 (d, J = 6.0 Hz, 1H), 6.17 (d, J = 5.7 Hz, 1H), 3.28 (s, 6H),

2.49 (s, 2H); ^{13}C-NMR (200 Hz) δ = 203.6, 156.7, 135.1, 106.4, 50.2, 44.9, Ms (CI) for $C_7H_{10}O_3$: m/z = 142 $(M)^+$, 160 $(M + NH_4^+)$.

8,8-Dimethyl-6,10-dioxa-spiro[4.5]dec-3-en-2-one (7b). Purification by column chromatography (SiO_2 hexane/diethyl ether, 1:1, Rf = 0.32) gave 1.03 g (28%) of **7b** as a white solid. Mp: 66-67°C; ^{1}H-NMR (300 MHz) δ = 7.54 (d, *J* = 6.0 Hz, 1H), 6.21 (d, *J* = 6.0 Hz, 1H), 3.60 (d, *J* = 16.0 Hz, 2H), 3.50 (d, *J* = 16.0 Hz, 2H), 2.60 (s, 2H), 1.09 (s, 3H), 0.89 (s, 3H); ^{13}C-NMR (200 MHz) δ = 204.1, 157.1, 135.3, 103.9, 72.9, 44.0, 29.9, 22.3, 22.2; HRMS calc. for $C_{10}H_{14}O_3$ 182.094, found 182.094; Anal.Calc. for $C_{10}H_{14}O_3$: C, 65.90; H, 7.74 found C, 65,98; H, 7.79.

1,4-Dioxa-spiro[4.4]non-8-en-7-one (7c). Purification by column chromatography (SiO_2 hexane/diethyl ether, 1:2, Rf = 0.32) gave 907 mg (22%) of **7c** as a colorless liquid. ^{1}H-NMR (300 MHz) δ = 7.20 (d, *J* = 6.0 Hz, 1H), 6.17 (d, *J* = 6.0 Hz, 1H), 4.02 (m, 4H), 2.57 (s, 2H); ^{13}C-NMR (200 MHz) δ = 204.2, 156.5, 135.6, 111.9, 65.4, 45.4; Ms (CI) for $C_7H_8O_3$: m/z = 140 (M^+), 158 $(M + NH_4^+)$.

2,2,3,3-Tetramethyl-1,4-dioxa-spiro[4.4]non-8-en-7-one (7e). Purification by column chromatography (SiO_2 hexane/diethyl ether, 1:4, Rf = 0.38) gave 1.143 g (29%) of **7e** as a white solid. Mp: 59-60°C; ^{1}H-NMR: (300 MHz) δ = 7.17 (d, *J* = 6.0 Hz, 1H), 6.14 (d, *J* = 6.0 Hz, 1H), 2.60, (s, 2H) 1.25 (s, 6H), 1.23 (s, 6H); ^{13}C-NMR: (200 MHz) δ = 204.9, 159.6, 135.1, 109.0, 83.8, 48.4, 23.4, 23.2; Ms (CI) for $C_{11}H_{16}O_3$: m/z = 197 (M^+) 214 $(M + NH_4^+)$.

General procedure for the 1,4-addition (8-10). A solution of $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) and phosphoramidite (0.02 mmol) in toluene (7 ml) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. The cyclopenten-3,5-dione monoacetal (0.5

mmol) was added and after cooling the reaction mixture to -45 °C, the diorganozinc compound (0.6 ml of a 1 M solution in toluene) was added and stirring at -45°C was continued for 18 h. The conversion was determined by TLC. After complete conversion, the reaction mixture was poured in 25 ml NH_4Cl (aq) and the organic layer was separated, and the aqueous layer was extracted two times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

(4*R*)-4-Ethyl-8,8-dimethyl-6,10-dioxa-spiro[4.5]decane-2-one (8). Purification by column chromatography (SiO_2 pentane/diethyl ether, 7:1, Rf = 0.6) gave 33 mg (31%) of **8** as a colorless liquid. ^{1}H-NMR (300 MHz) δ = 3.45 (s, 4H), 2.96 (d, J = 18.0 Hz, 1H), 2.49 (dd, J = 17.7 Hz, J = 17.4 Hz, 1H), 2.35 (d, J = 18.0 Hz, 1H), 2.22 (m, 1H), 2.07 (dd, J = 17.7 Hz, J =17.2 Hz, 1H), 1.89 (m, 1H), 1.39 (m, 1H), 1.16 (s, 3H), 0.94 (t, J = 7.8 Hz, 3H), 0.76 (s, 3H); ^{13}C-NMR (200 MHz) δ = 213.5, 104.1, 72.8, 71.3, 47.7, 44.3, 42.7, 30.2, 22.6, 22.0, 20.6, 12.5; HRMS calc. for $C_{12}H_{20}O_3$ 212.141 found 212.143.

(4*R*)-4-Ethyl-8,8-diphenyl-6,10-dioxa-spiro[4.5]decane-2-one (9). Purification by column chromatography (SiO_2 pentane/diethyl ether, 3:1, Rf = 0.24) gave 52 mg (31%) of **9** as a colorless liquid.^{1}H-NMR (300 MHz) δ = 7.47-7.06 (m, 10H), 4.59 (d, J = 11.6 Hz, 2H), 4.26 (m, 2H), 3.07 (d, J = 18.0 Hz, 1H), 2.60-2.05 (m, 4H), 1.59 (m, 1H), 1.30 (m, 1H), 0.80 (t, J = 7.4 Hz, 3H); ^{13}C-NMR (200 MHz) δ = 213.1, 143.7, 143.4, 128.7, 128.5, 128.1, 126.9, 126.4, 126.3, 104.7, 70.7, 68.8, 47.5, 44.8, 44.7, 42.8, 20.6, 12.4; HRMS calc. for $C_{22}H_{24}O_3$ 336.172, found 336.172; The ee was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*PrOH:hexane 10:90, 1 ml/min, RT, T_r = 6.71 min, T_r = 13.77 min)

4-Ethyl-3-(2-hydroxy-8,8-dimethyl-6,10-dioxaspiro[4.5]dec-3-en-2-yl)-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one (8b). Purification by column chromatography (SiO_2 pentane/diethyl ether, 2:3, Rf = 0.42) gave 12 mg (12%) of **8b** as a colorless liquid. ^{1}H-NMR (500 MHz) δ = 6.12 (d, *J* = 5.8 Hz, 1H), 5.98 (d, *J* = 5.8 Hz, 1H), 3.49 (m, 8H), 2.96 (d, *J* = 14.2 Hz, 1H), 2.82 (d, *J* = 18.0 Hz, 1H), 2.59 (d, *J* = 18.0 Hz, 1H), 2.42 (q, *J* = 6.3 Hz, 1H), 2.38 (d, *J* = 6.0 Hz, 1H), 2.08 (d, *J* = 14.2 Hz, 1H), 1.91 (m, 1H), 1.26 (m, 1H), 1.16 (s, 3H), 1.02 (s, 3H), 0.98 (t, *J* = 7.8 Hz, 3H), 0.92 (s, 3H), 0.81 (s, 3H); ^{13}C-NMR (200 MHz) δ = 213.8, 139.9, 132.1, 106.9, 103.5, 83.1, 72.7, 72.4, 72.0, 71.8, 60.9, 48.1, 46.0, 45.4, 30.0, 23.1, 22.8, 22.4, 22.1, 12.4; Ms (EI) for $C_{22}H_{34}O_6$: m/z = 395 (M^+).

4-Ethyl-3-(2-hydroxy-8,8-dimethyl-6,10-dioxaspiro[4.5]dec-3-en-2-yl)-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one (8a). Purification by column chromatography (SiO_2 pentane/diethyl ether, 7:1, Rf = 0.38) gave 30 mg (30%) of **8a** as a colorless liquid. ^{1}H-NMR (500 MHz) δ = 6.30 (d, *J* = 5.8 Hz, 1H), 6.18 (d, *J* = 5.8 Hz, 1H), 3.52 (m, 8H), 2.92 (dd, *J* = 17.4 Hz, *J* = 0.9 Hz, 1H), 2.54 (d, *J* = 17.4 Hz, 1H), 2.47 (d, *J* = 8.1 Hz, 1H), 2.31 (q, *J* = 8.1 Hz, 1H), 2.27 (d, *J* = 14.0 Hz, 1H), 2.16 (d, *J* = 14.0 Hz, 1H), 1.91 (m, 1H), 1.36 (m, 1H), 1.15 (s, 3H), 1.00 (t, *J* = 7.8 Hz, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 0.77 (s, 3H); ^{13}C-NMR (200 MHz) δ = 213.8, 139.9, 132.1, 106.9, 103.5, 83.1, 72.7, 72.4, 72.0, 71.8, 60.9, 48.1, 46.0, 45.4, 30.0, 23.1, 22.8, 22.4, 22.1, 12.4; Ms (EI) for $C_{22}H_{34}O_6$: m/z = 395 (M^+).

General procedure for the tandem 1,4-addition-aldol reaction (11a, 11b, 13a-21a). A solution of $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) and phosphoramidite[1] (0.02 mmol) in toluene (7 ml) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. Cyclopenten-3,5-dione monoacetal (0.5 mmol) and the aldehyde (0.5 mmol) were added. After cooling the reaction mixture to -45 °C, the dialkylzinc reagent (0.6 ml, 1M solution in toluene) was added and stirring at -45°C was continued for 18 h. After complete conversion, the reaction mixture was poured in 25 ml NH_4Cl (aq), the organic layer was separated, and the aqueous layer was extracted two times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

(3*S*,4*R*)-4-Ethyl-3-[(*R*)-hydroxy(phenyl)methyl]-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one (13a). Purification by column chromatography (SiO_2 hexane/diethyl ether, 1:2, Rf = 0.32) gave 107 mg (67%) of **13a** as a colorless oil which solidified upon standing. ^{1}H-NMR (300 MHz) δ = 7.28-7.23 (m, 5H), 4.75 (d, J = 8.1 Hz, 1H), 3.50 (s, 2H), 3.37 (d, J = 2.0 Hz, 2H), 2.74 (dd, J = 18.0 Hz, J = 1.2 Hz, 1H), 2.50 (d, J = 18 Hz, 1H), 2.46 (t, J = 7.5 Hz, 1H), 2.00 (q, J = 6.3 Hz, 1H), 1.55 (m, J = 6.3 Hz, 2H), 1.02 (s, 3H), 0.79 (s, 3H), 0.57 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (300 MHz) δ = 216.4, 140.8, 128.0, 127.7, 126.7, 103.2, 74.9, 71.7, 71.3, 59.1, 47.7, 44.7, 29.6, 22.2, 21.7, 20.6, 11.4; HRMS calc. for $C_{19}H_{26}O_4$ 318.183, found 318.183

(3*S*,4*R*)-4-Butyl-3-[(*R*)-hydroxy(phenyl)methyl]-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one (14a). Purification by column chromatography (SiO_2

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hexane/diethyl ether, 1:1, Rf = 0.33) gave 111 mg (64%) of **14a** as a colorless oil which solidified upon standing. ^{1}H-NMR (300 MHz) δ = 7.31- 7.26 (m, 5H), 4.75 (d, *J* = 8.1 Hz, 1H), 3.97 (d, *J* = 1.5 Hz, 1H(OH)), 3.44 (s, 2H), 3.37 (d, *J* = 4.4 Hz, 2H), 2.86 (dd, *J* = 18.0 Hz, *J* = 1.2 Hz, 1H), 2.54 (d, *J* = 18.0 Hz, 1H), 2.40 (t, *J* = 7.5 Hz, 1H), 2.03 (q, *J* = 6.3 Hz, 1H), 1.52 (m, *J* = 6.6 Hz, 1H), 1.03 (s, 3H), 0.94 (m, 5H), 0.80 (s, 3H), 0.66 (m, 3H); ^{13}C-NMR (200 MHz) δ = 216.8, 141.0, 128.3, 128.1, 127.0, 103.5, 75.3, 72.1, 71.6, 59.9, 46.4, 45.1, 30.0, 29.5, 27.9, 22.6, 22.1, 21.6, 13.9; HRMS calc. for $C_{21}H_{30}O_4$ 346.214, found 346.213.

(3*S*,4*R*)-4-Ethyl-3-[(*R*)-hydroxy(phenyl)methyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (15a). Purification by column chromatography (SiO_2 pentane/diethyl ether, 2:1, Rf = 0.18) gave 167 mg (76%) of **15a** as a colorless oil which solidified upon standing. ^{1}H-NMR (300 MHz) δ = 7.31-7.02 (m, 15H), 4.74 (dd, *J* = 7.8 Hz, *J* = 1.8 Hz, 1H), 4.76-4.13 (m, 4H), 3.77 (d, *J* = 1.8 Hz, 1H(OH)), 2.52 (d, *J* = 18.0 Hz, 1H), 2.50 (d, *J* = 17.7 Hz, 1H), 2.40 (t, *J* = 7.2 Hz, 1H), 1.93 (q, *J* = 7.2 Hz, 1H), 1.37 (m, *J* = 7.2 Hz, 1H), 0.76 (m, *J* = 7.2 Hz, 1H), 0.31 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (200 MHz) δ = 216.2, 205.8, 143.5, 143.3, 141.0, 128.6, 128.3, 128.3, 218.1, 127.9, 126.9, 126.7, 126.5, 125.8, 104.2, 75.2, 69.9, 69.1, 59.4, 48.0, 45.6, 44.9, 20.9, 11.7; Ms (CI) for $C_{29}H_{30}O_4$: m/z = 442 (M^+), 460 ($M + NH_4^+$).

(3*S*,4*R*)-3-[(*R*)-(4-Bromophenyl)(hydroxy)methyl]-4-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (17a). Purification by column chromatography (SiO_2 pentane/diethyl ether, 2:1, Rf = 0.31) gave 179 mg (69%) of **17a** as a colorless oil which solidified upon standing. ^{1}H-NMR: (300 MHz) δ = 7.42-7.06 (m, 14H), 4.76 (d, *J* = 7.8 Hz, 1H), 4.51-4.17 (m, 4H), 2.96 (d, *J* = 18.0 Hz, 1H), 2.57 (d, *J* = 18.0 Hz, 1H), 2.40 (t,

J = 7.2 Hz, 1H), 1.94 (q, J = 7.2 Hz, 1H), 1.50 (m, J = 7.2 Hz, 1H), 0.85 (m, J = 7.2 Hz, 1H), 0.39 (t, J = 7.2 Hz, 3H); ^{13}C-NMR: (200 MHz) δ = 215.8, 143.4, 143.2, 140.1, 131.5, 128.6, 128.6, 128.3, 127.9, 126.9, 126.7, 126.5, 121.9, 104.1, 74.5, 69.9, 69.1, 59.2, 48.1, 45.4, 44.9, 20.9, 11.7; HRMS calc. for $C_{29}H_{29}O_4Br$ 520.124, found 520.123.

(3*S*,4*R*)-3-[(*R*)-(4-Bromophenyl)(hydroxy)methyl]-4-butyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (11a). Purification by column chromatography (SiO_2 pentane/diethyl ether, 2:1, Rf = 0.28) gave 169 mg (62%) of **11a** (major product) as colorless oil which solidified upon standing. ^{1}H-NMR: (300 MHz) δ = 7.42- 7.05 (m, 14H), 4.75 (dd, J = 7.8 Hz, J = 1.8 Hz, 1H), 4.53-4.46 (m, 2H), 4.31-4.16 (m, 2H), 3.84 (d, J = 1.8 Hz, 1H (OH)), 3.03 (dd, J = 18.0 Hz, J = 1.8 Hz, 1H), 2.53 (d, J = 18.3 Hz, 1H), 2.39 (dd, J = 7.5 Hz, J = 7.2 Hz, 1H), 2.02 (q, J = 7.2 Hz, 1H), 1.40 (m, 1H), 0.84-0.69 (m, 5H), 0.57 (t, J = 7.2 Hz, 3H); ^{13}C-NMR: (200 MHz) δ = 215.9, 143.3, 143.1, 140.1, 131.4, 128.7, 128.6, 128.3, 127.9, 126.9, 126.6, 126.4, 121.9, 103.9, 74.4, 70.1, 68.9, 59.6, 47.0, 45.2, 44.8, 29.6, 27.6, 22.7, 13.7; Ms (EI) for $C_{31}H_{33}BrO_4$: m/z = 550 (M^+). (For NOESY-NMR see supporting material)

(3*S*,4*R*)-3-[(*S*)-(4-Bromophenyl)(hydroxy)methyl]-4-butyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (11b). Purification by column chromatography (SiO_2 pentane/diethyl ether, 2:1, Rf = 0.24) gave 4 mg (1.5%) of **11b** (minor product) as colorless oil which solidified upon standing: ^{1}H-NMR: (300 MHz) δ = 7.42- 7.00 (m, 14H), 5.11 (dd, J = 6.6 Hz, J = 3.6 Hz, 1H), 4.55 (m, 2H), 4.28-4.12 (m, 2H), 3.49 (d, J = 6.6 Hz, 1H (OH)), 3.05 (dd, J = 17.7 Hz, J = 1.8 Hz, 1H), 2.50 (dd, J = 9.3 Hz, J = 3.6 Hz, 1H), 2.30 (d, J = 17.7 Hz, 1H), 2.15 (q, J = 7.2 Hz, 1H), 1.39 (m, 1H), 0.86- 0.67 (m, 5H), 0.55 (t, J = 7.2 Hz, 3H); ^{13}C-NMR: (200 MHz) δ = 214.5, 143.2, 143.0, 140.9,

131.4, 128.7, 128.3, 128.1, 127.6, 127.0, 126.4, 121.3, 103.9, 72.1, 70.5, 68.7, 60.0, 45.2 (two peaks), 44.7, 29.7, 27.5, 22.9, 13.7; Ms (EI) for $C_{31}H_{33}BrO_4$: m/z = 550 (M^+).(For NOESY-NMR see supporting material)

(3*S*,4*R*)-4-Ethyl-3-[(1*S*)-1-hydroxybutyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (18a). Purification by column chromatography (SiO_2 pentane/diethyl ether, 3:2, Rf = 0.23) gave 133 mg (65%) of **18a** as a colorless oil which solidified upon standing; ^{1}H-NMR: (300 MHz) δ = 7.41-7.02 (m, 10H), 4.55 (m, 2H), 4.31-4.14 (m, 2H), 3.67 (q, *J* = 4.8 Hz, 1H), 3.04 (dd, *J* = 17.7 Hz, *J* = 1.2 Hz, 1H), 2.47 (d, *J* = 17.7 Hz, 1H), 2.41 (d, *J* = 5.1 Hz, 1H(OH)), 2.20 (m, 2H), 1.72- 1.20 (m, 7H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.71 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR: (200 MHz) δ = 214.9, 143.5, 143.2, 128.7, 128.3, 128.2, 126.9, 126.5, 126.3, 103.8, 71.4, 70.4, 68.8, 58.0, 49.4, 45.5, 44.7, 37.7, 20.8, 19.1, 13.9, 12.5; HRMS calc. for $C_{26}H_{32}O_4$ 408.230, found 408.232.

(8*S*,9*R*)-9-Ethyl-8-[(*R*)-hydroxy(phenyl)methyl]-2,2,3,3-tetramethyl-1,4-dioxaspiro[4.4]nonan-7-one (19a). Purification by column chromatography (SiO_2 pentane/diethyl ether, 2:1, Rf = 0.36) gave 90 mg (54%) of **19a** as a colorless oil. ^{1}H-NMR (300 MHz) δ = 7.35-7.22 (m, 5H), 4.85 (d, *J* = 9.6 Hz, 1H), 2.74 (d, *J* = 18.0 Hz, 1H), 2.52 (d, *J* = 18.0 Hz, 1H), 2.36 (d, *J* = 9.3 Hz, 1H), 1.68 (m, 1H), 1.20 (s, 3H), 1.19 (s, 3H), 1.17 (m, 1H), 1.16 (s, 3H), 1.12 (s, 3H), 0.92 (m, 1H), 0.40 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR: (200 MHz) δ = 218.1, 141.1, 128.2, 128.0, 127.4, 110.4, 83.5, 83.3, 74.8, 60.4, 52.3, 50.5, 23.7, 23.5, 11.1; Ms (CI) for $C_{20}H_{28}O_4$: m/z = 332 (M^+), 350 ($M+NH_4^+$).

(8*S*,9*R*)-9-Ethyl-8-[(*R*)-hydroxy(phenyl)methyl]-1,4-dioxaspiro[4.4]nonan-7-one (20a). Crude product; ^{1}H-NMR (300 MHz) δ = 7.37-7.34 (m, 5H), 4.68 (d, *J* = 8.6 Hz, 1H), 3.95 (m, 4H), 2.68 (d, *J* = 13.6 Hz, 1 H), 2.50 (d, *J* = 13.6 Hz, 1 H), 2.49 (t, 1H),

1.92 (q, J = 6.2 Hz, 1H), 1.52 (m, J = 6.5 Hz, 1H), 0.93 (m, J = 6.5 Hz, 1H), 0.59 (t, J = 7.2 Hz, 3H); ^{13}C NMR (200 MHz) δ = 216.6, 140.9, 128.4, 128.1, 127.0, 112.9, 75.0, 65.0, 64.3, 60.5, 48.3, 48.1, 22.0, 11.7; Ms (CI) for $C_{16}H_{20}O_4$: m/z = 276 (M^+), 294 ($M+NH_4^+$).

(2*S*,3*R*)-3-Ethyl-2-[(*R*)-hydroxy(phenyl)methyl]-4,4-dimethoxycyclopentanone (21a). Crude product; ^{1}H-NMR (300 MHz) δ = 7.34-7.19 (m, 5H), 4.72 (d, J = 9.6 Hz, 1H), 3.16 (d, J = 9.9 Hz, 6H), 2.61 (d, J = 17.7 Hz, 2H), 2.32 (m, 1H), 1.81, (m, 1H), 1.50 (m, 1H), 0.91 (m, 1H), 0.34 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (200 MHz) δ = 217.1, 140.9, 128.2, 128.0, 127.3, 106.5, 75.5, 60.1, 50.1, 48.2, 46.0, 45.6, 23.2, 10.8; Ms (CI) for $C_{16}H_{22}O_4$: m/z = 278 (M^+), 296 ($M+NH_4^+$).

General procedure for the oxidation to a diketone (11c, 13c-17c). To hydroxy ketone (0.2 mmol) in CH_2Cl_2 (5 ml) were added molecular sieves (4 Å, 0.5 g) and PCC (215 mg, 1 mmol) at 0°C. The reaction mixture was stirred for 4h at room temperature and diluted with diethyl ether, filtered over celite and evaporated to dryness.

(3*R*,4*R*)-3-Benzoyl-4-ethyl-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one (13c). Purification by column chromatography (SiO_2 hexane/diethyl ether, 2;1, Rf = 0.33) gave 40 mg (64%) of **13c** as a colorless oil which solidified upon standing. ^{1}H-NMR (300 MHz) δ = 7.99 (d, J = 6.0 Hz, 2H), 7.57-7.43 (m, 3H), 4.26 (d, J = 11.4 Hz, 1H), 3.58-3.44 (m, 4H), 3.25 (d, J = 17.7 Hz, 1H), 3.14 (m, 1H), 2.43 (d, J = 17.4 Hz, 1H), 1.97 (m, 1H), 1.54 (m, 1H), 1.22 (s, 3H), 0.77 (t, J = 7.5 Hz, 3H), 0.75 (s, 3H); ^{13}C-NMR (200 MHz) δ = 207.1, 195.2, 137.1, 133.5, 129.5, 128.7, 102.5, 73.5, 71.2, 62.3, 50.9, 44.6, 30.1, 22.6, 21.9, 20.1, 12.9; HRMS calc. for $C_{19}H_{24}O_4$ 316.168, found 316.167; the ee of

87 % was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*PrOH:hexane 3:97, 1 ml/min, RT, T_r = 17.0 min, T_r = 20.9 min).

(3*R*,4*R*)-3-Benzoyl-4-butyl-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one (14c). Purification by column chromatography (SiO_2 hexane/diethyl ether, 5:2, Rf = 0.38) gave 43 mg (63%) of **14c** as a colorless oil which solidified upon standing. ^{1}H-NMR (300 MHz) δ = 7.98 (d, *J* = 7.5 Hz, 2H), 7.50 (m, 3H), 4.26 (d, *J* = 11.0 Hz, 1H), 3.45 (m, 4H), 3.25 (d, *J* = 17.0 Hz, 1H), 2.43 (d, *J* = 17.0 Hz, 1H), 1.92 (m, 1H), 1.46 (m, 1H), 1.22 (m, 7H), 1.04 (m, 1H), 0.77 (t, *J* = 7 Hz, 3H), 0.75 (s, 3H); ^{13}C-NMR (200 MHz) δ = 207.0, 194.9, 137.1, 133.4, 129.4, 128.6, 102.5, 73.5, 71.2, 62.7, 49.2, 44.5, 30.5, 30.2, 26.9, 22.9, 22.8, 22.0, 13.9; HRMS calc. for $C_{21}H_{28}O_4$ 344.198, found 344.199; the ee of 87 % was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, iPrOH:hexane 10:90, 1ml/min, RT, T_r = 7.8 min, T_r = 11.1)

(3*R*,4*R*)-3-Benzoyl-4-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (15c). Purification by column chromatography (SiO_2 pentane/diethyl ether, 5:1, Rf = 0.30) gave 67 mg (76%) of **15c** as a colorless oil which solidified upon standing. ^{1}H-NMR (300 MHz) δ = 7.99 (d, *J* = 6.0 Hz, 2H), 7.57-7.03 (m, 13H), 4.65 (d, *J* = 11.7 Hz, 2H), 4.35-4.21 (m, 3H), 3.37 (d, *J* = 17.7 Hz, 1H), 3.11 (m, 1H), 2.56 (d, *J* = 17.1 Hz, 1H), 1.59 (m, 1H), 1.30 (m, 1H), 0.57 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (200 MHz) δ = 206.6, 194.8, 143.4, 143.1, 136.9, 133.5, 129.4, 128.7, 128.6, 128.1, 127.0, 126.3, 103.0, 71.4, 68.6, 62.4, 50.8, 45.1, 44.7, 20.1, 12.8; enol form <1%; HRMS calc. for $C_{29}H_{28}O_4$ 440.198, found 440.197. The ee of 94 % was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*PrOH:hexane 50:50, 1 ml/min, RT, T_r = 5.64 min, T_r = 13.11 min).

(3*R*,4*R*)-3-(4-Bromobenzoyl)-4-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (17c). Purification by column chromatography (SiO_2 pentane/diethyl ether, 5:1, Rf = 0.36) gave 77 mg (76%) of **17c** as a colorless oil which solidified upon standing. ^{1}H-NMR (300 MHz) δ = 7.83 (d, *J* = 8.4 Hz, 2H), 7.63-7.03 (m, 12H), 4.65 (d, *J* = 12.0 Hz, 2H), 4.44-4.16 (m, 4H), 3.36 (d, *J* = 17.4 Hz, 1H), 3.11 (m, 1H), 2.54 (d, *J* = 17.1 Hz, 1H), 1.59 (m, 1H), 1.31 (m, 1H), 0.55 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (200 MHz) δ = 206.3, 193.7, 143.4, 143.0, 135.6, 131.9, 130.9, 129.0, 128.8, 128.6, 128.1, 127.1, 126.4, 126.3, 102.9, 71.4, 68.6, 62.4, 50.6, 45.0, 44.7, 20.1, 12.8; HRMS calc. for $C_{29}H_{27}O_4$ Br 518.109, found 518.107. The ee of 96 % was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*PrOH:hexane 50:50, 1 ml/min, RT, T_r = 6.7 min, T_r = 11.9 min).

(3*R*,4*R*)-3-(4-Bromobenzoyl)-4-butyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (11c). Purification by column chromatography (SiO_2 pentane/diethyl ether, 5:1, Rf = 0.30) gave 68 mg (62%) of **11c** as a colorless oil which solidified upon standing. ^{1}H-NMR (300 MHz) δ = 7.82-7.02 (m, 14H), 4.62 (d, *J* = 11.7 Hz, 2H), 4.41-4.13 (m, 2H), 3.33 (d, *J* = 17.7 Hz, 1H), 3.10 (m, 1H), 2.48 (d, *J* = 17.7 Hz, 1H), 1.51 (m, 1H), 1.22-0.74 (m, 5H), 0.62 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (200 MHz) δ = 206.3, 193.5, 143.2, 142.9, 135.6, 131.9, 130.9, 128.7, 128.6, 128.1, 127.1, 126.3, 126.2, 102.9, 71.4, 68.6, 62.7, 48.8, 44.9, 44.7, 30.2, 27.0, 22.8, 13.6; HRMS calc. for $C_{31}H_{31}O_4Br$ 548.138 found 548.139. The ee of 97 % was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*PrOH:hexane 50:50, 1 ml/min, RT, T_r = 5.70 min, T_r = 9.43 min).

(4*R*,5*S*)-4-Ethyl-3-(3-hydroxy-2,2-dimethylpropoxy)-5-[(*R*)-hydroxy(phenyl)methyl]-2-cyclopenten-1-one (13d). Purification by column

chromatography (SiO_2 MeOH/diethyl ether, 1:40, Rf = 0.37) gave 107 mg (67%) of **13d** as a white solid. ^{1}H-NMR (300 MHz) δ = 7.36-7.21 (m, 5H), 5.27 (s, 1H), 5.20 (s, 1H(OH)), 4.58 (d, *J* = 9.6 Hz, 1H), 3.78 (d, *J* = 9.2 Hz, 1H), 3.67 (d, *J* = 9.2 Hz, 1H), 3.41 (m, 2H), 2.39 (m, 2H), 1.51 (s, 3H), 1.21 (m, 1H), 0.93 (s, 3H), 0.87 (m, 1H), 0.46 (t, *J* = 7.5 Hz, 3H); HRMS calc. for $C_{19}H_{26}O_4$ 318.183, found 318.181.

(4*R*,5*S*)-4-Ethyl-3-(2-hydroxyethoxy)-5-[(*R*)-hydroxy(phenyl)methyl]-2-cyclopenten-1-one (20d). Purification by column chromatography (SiO_2 MeOH/diethyl ether, 1:30, Rf = 0.31) gave 104 mg (75%) of **20d** as a white solid. ^{1}H-NMR (300 MHz) δ = 7.35-7.21 (m, 5H), 5.30 (s, 1H), 5.10 (s, 1H(OH), 4.59 (d, *J* = 9.9 Hz, 1H), 4.04 (m, 2H), 3.91 (m, 2H), 2.41 (m, 2H), 1.20 (m, *J* = 7.2 Hz, 1H), 0.96 (m, 1H), 0.44 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (200 MHz) δ = 208.2, 192.4, 141.2, 128.4, 128.3, 127.0, 103.7, 76.4, 73.3, 60.3, 55.7, 44.0, 22.8, 8.9; HRMS calc. for $C_{16}H_{20}O_4$ 276.135, found 276.136.

exp1 relayh

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	sw-160301.fid	dmm	c
ACQUISITION		dmf	9000
sfrq	499.861	dseq	
tn	H1	dres	1.0
at	0.228	homo	n
np	2048	PROCESSING	
sw	4482.8	sb	0.114
fb	2600	sbs	not used
ss	2	wtfile	
tpwr	60	proc	ft
pw	16.0	fn	2048
p1	16.0	math	f
d1	1.000		
tof	-689.6	werr	
nt	4	wexp	
ct	4	wbs	
tau	0	wnt	
relay	0	2D PROCESSING	
alock	n	sb1	0.029
gain	26	sbs1	not used
FLAGS		wtfile1	
il	n	proc1	ft
in	n	fn1	2048
dp	y		
hs	nn		
2D ACQUISITION			
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ni	256		
phase	1		
DISPLAY			
sp	374.5		
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sc	6		
wc	100		
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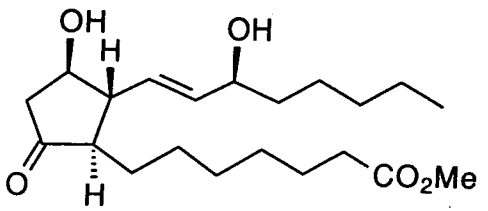
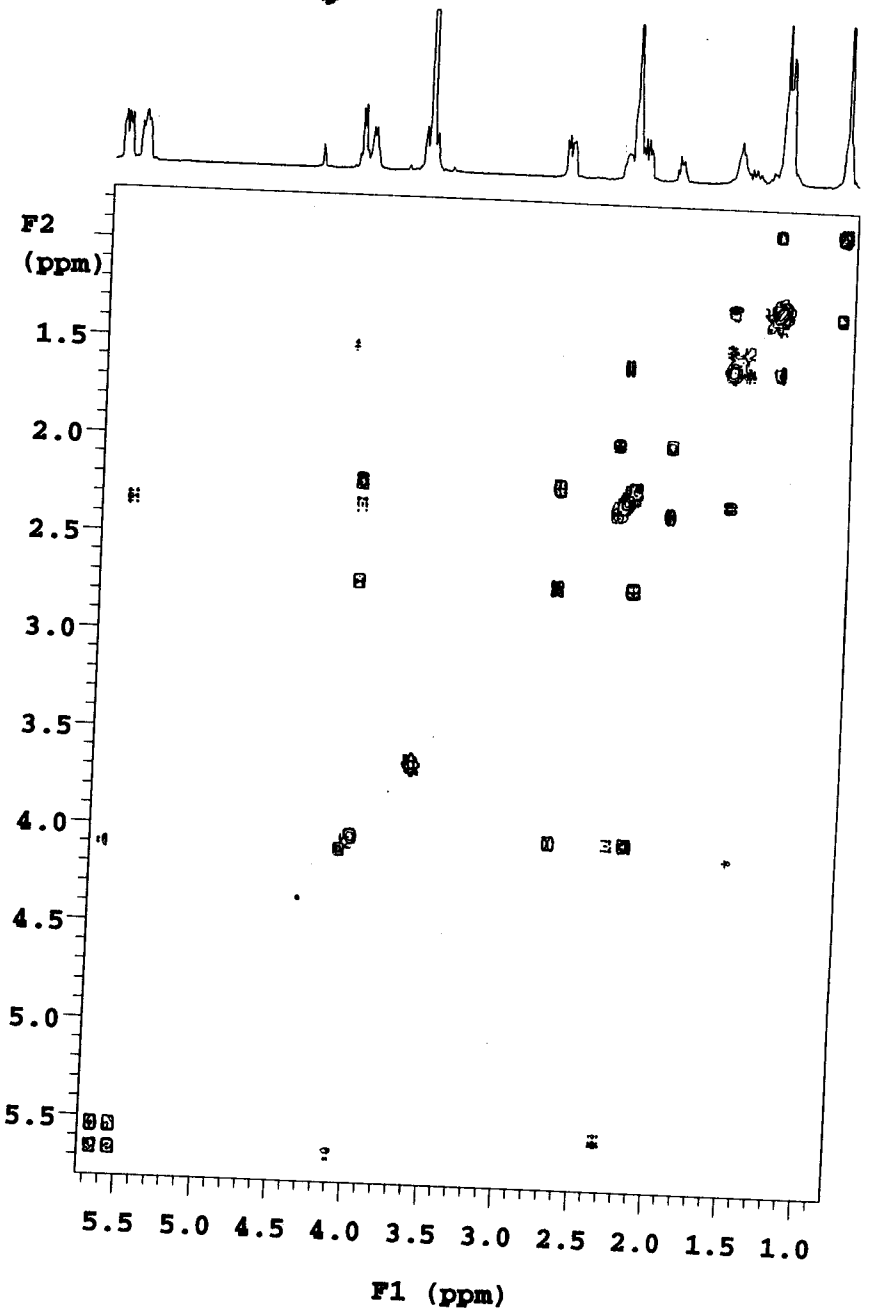
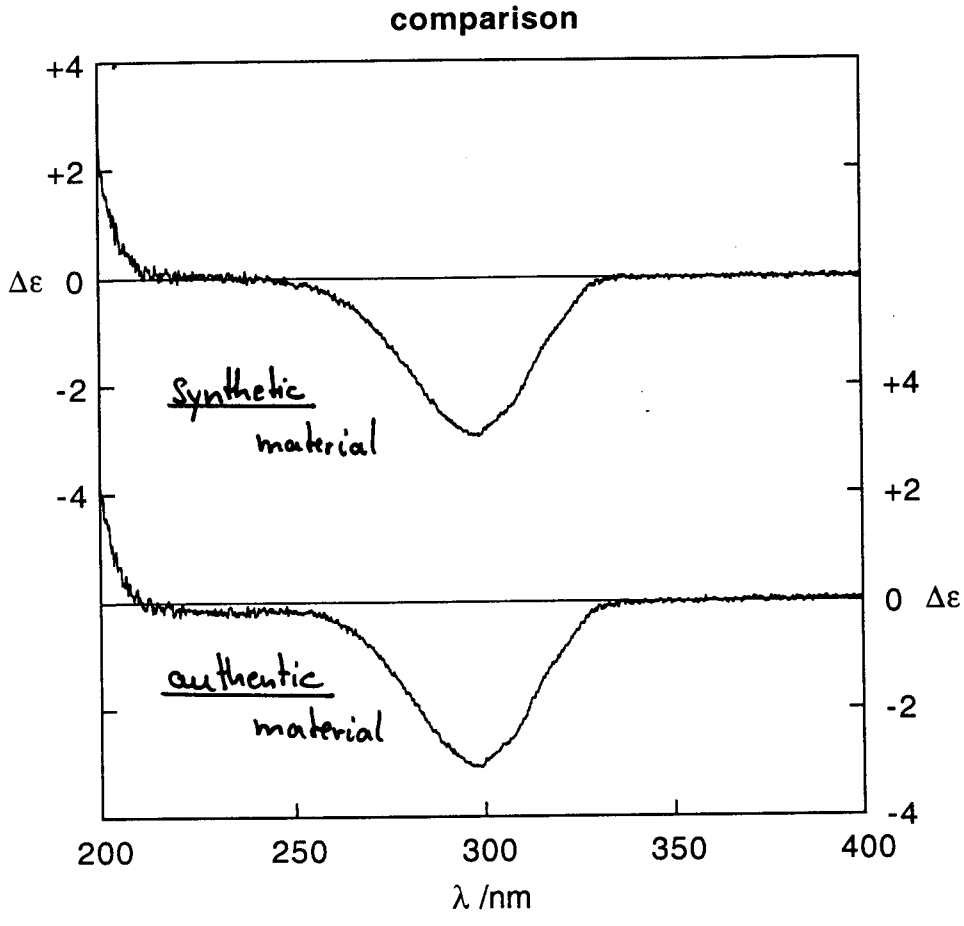
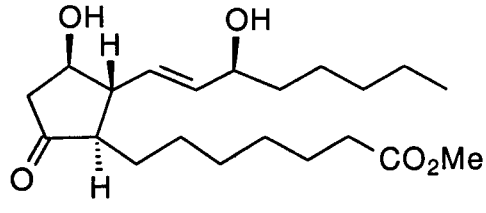
Prostaglandin E1 methyl ester (28)

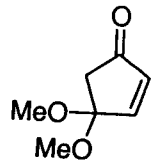




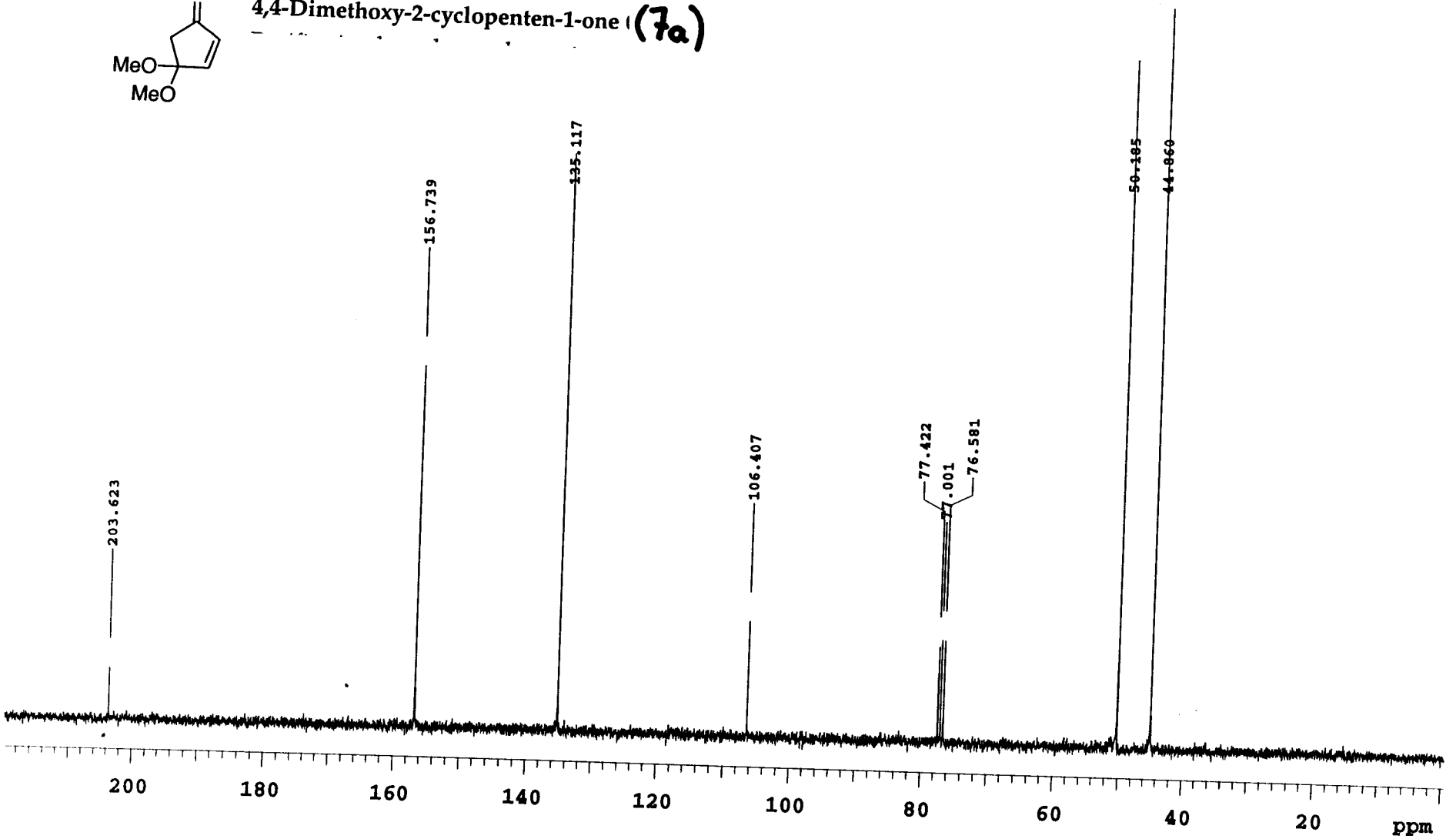


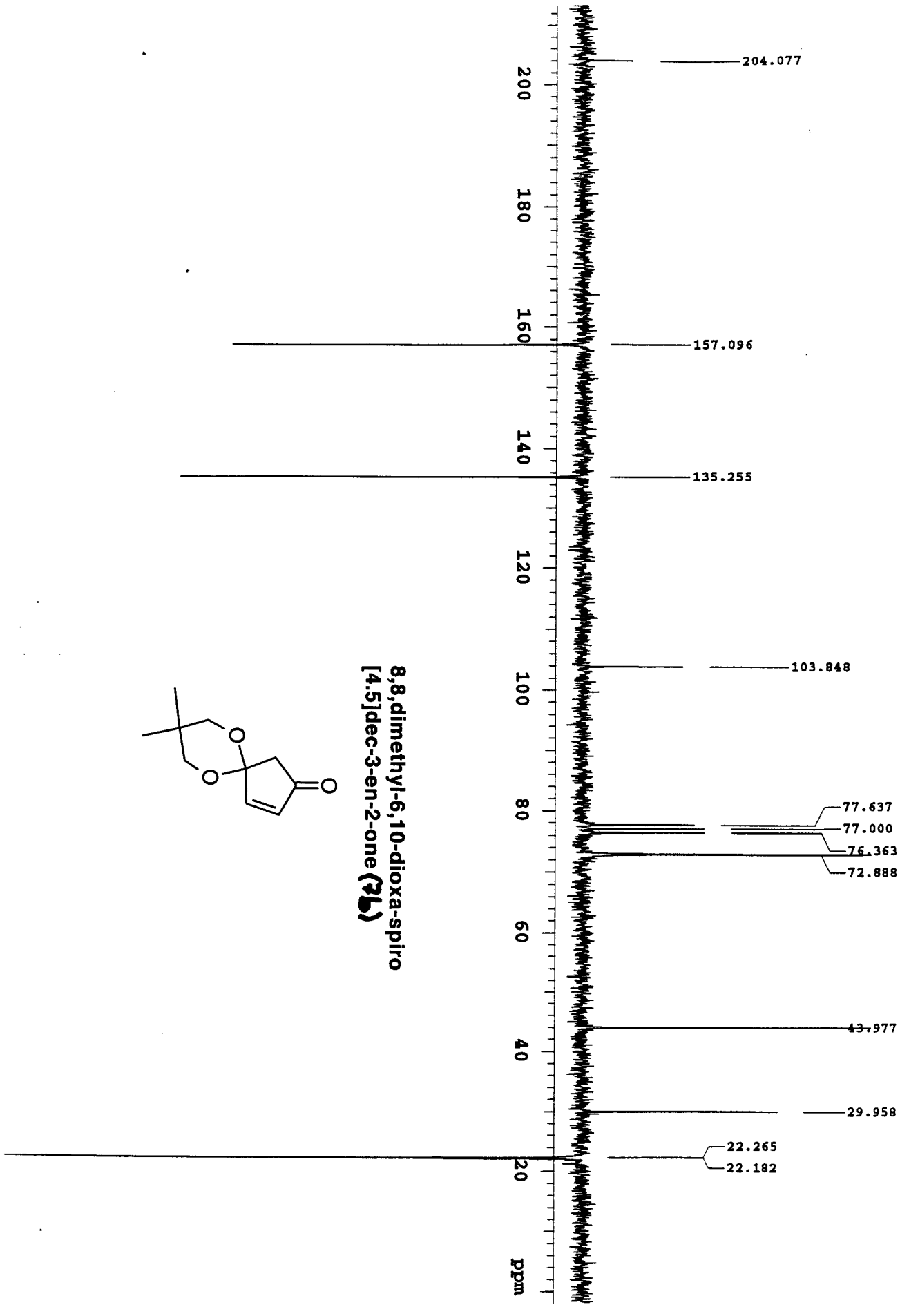
Prostaglandin E1 methyl ester (28)





4,4-Dimethoxy-2-cyclopenten-1-one (7a)

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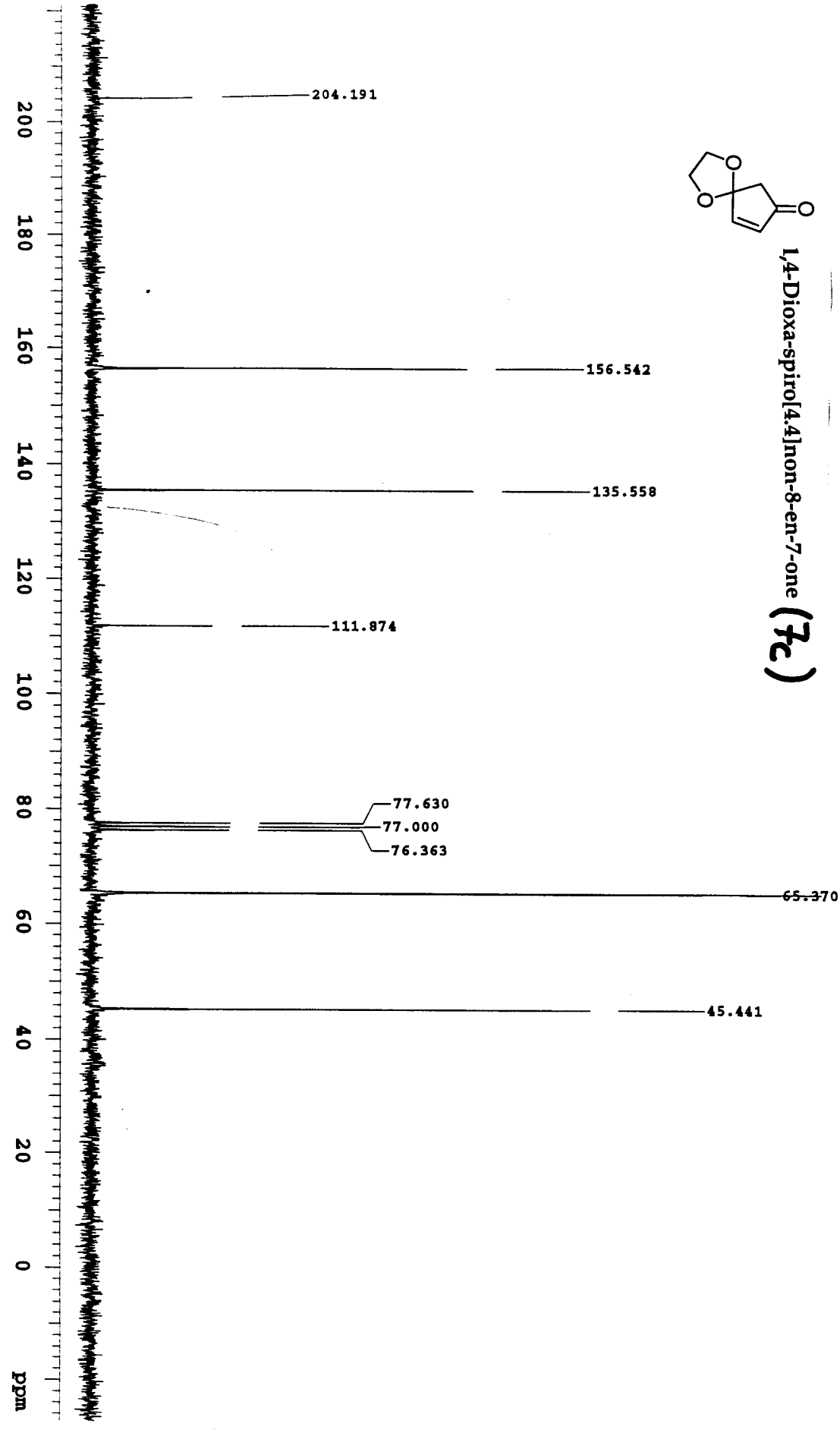
157.096
135.255
103.848
77.637
77.000
76.363
72.888
43.977
29.958
22.265
22.182
200
180
160
140
120
100
80
60
40
20
ppm
8,8,dimethyl-6,10-dioxa-spiro
[4.5]dec-3-en-2-one (7b)


1,4-Dioxa-spiro[4.4]non-8-en-7-one (7c)
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156.542
135.558
111.874
77.630
77.000
76.363
65.370
45.441
200
180
160
140
120
100
80
60
40
20
0
ppm

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1	15332.909	203.267	14.7
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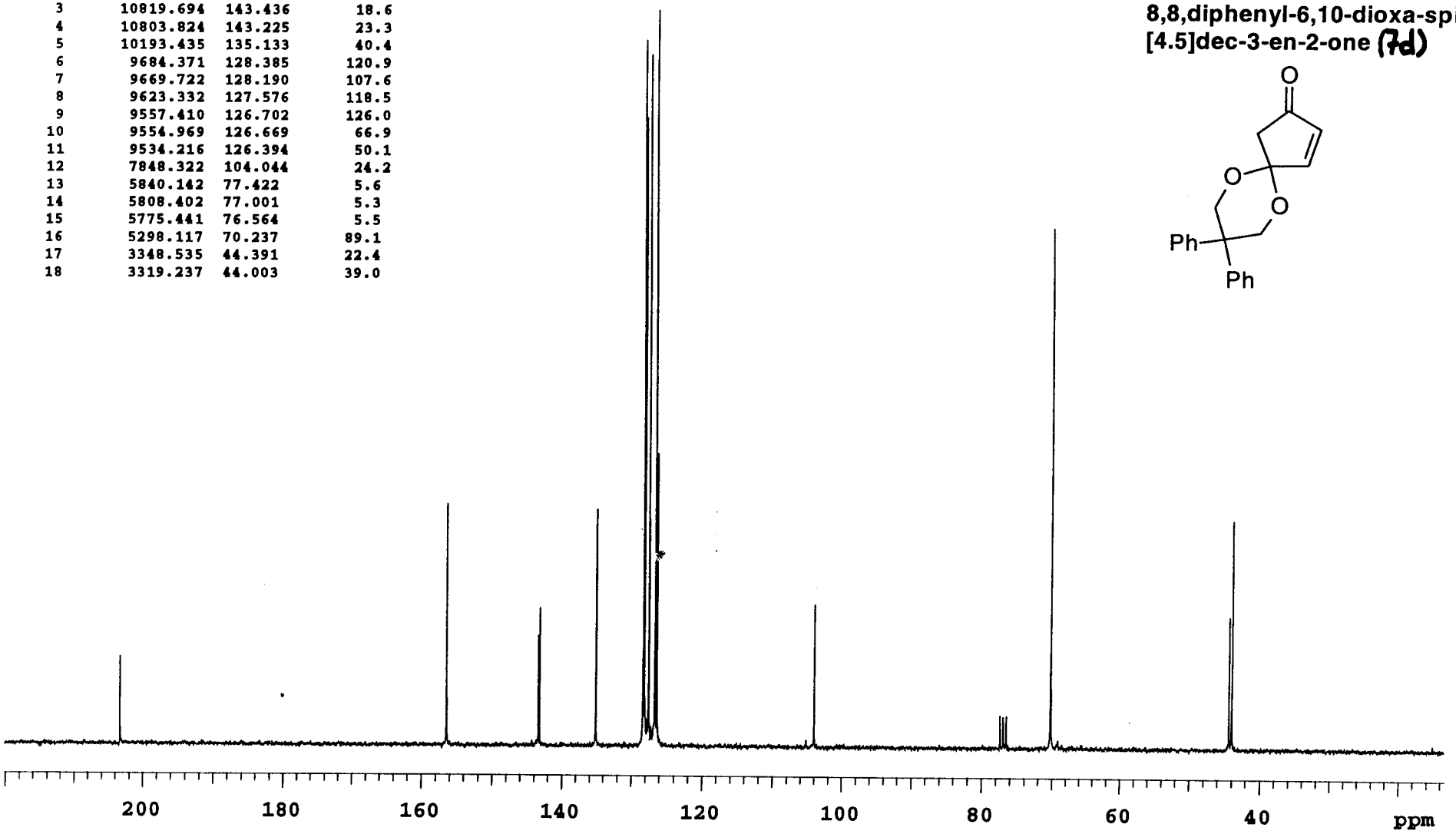
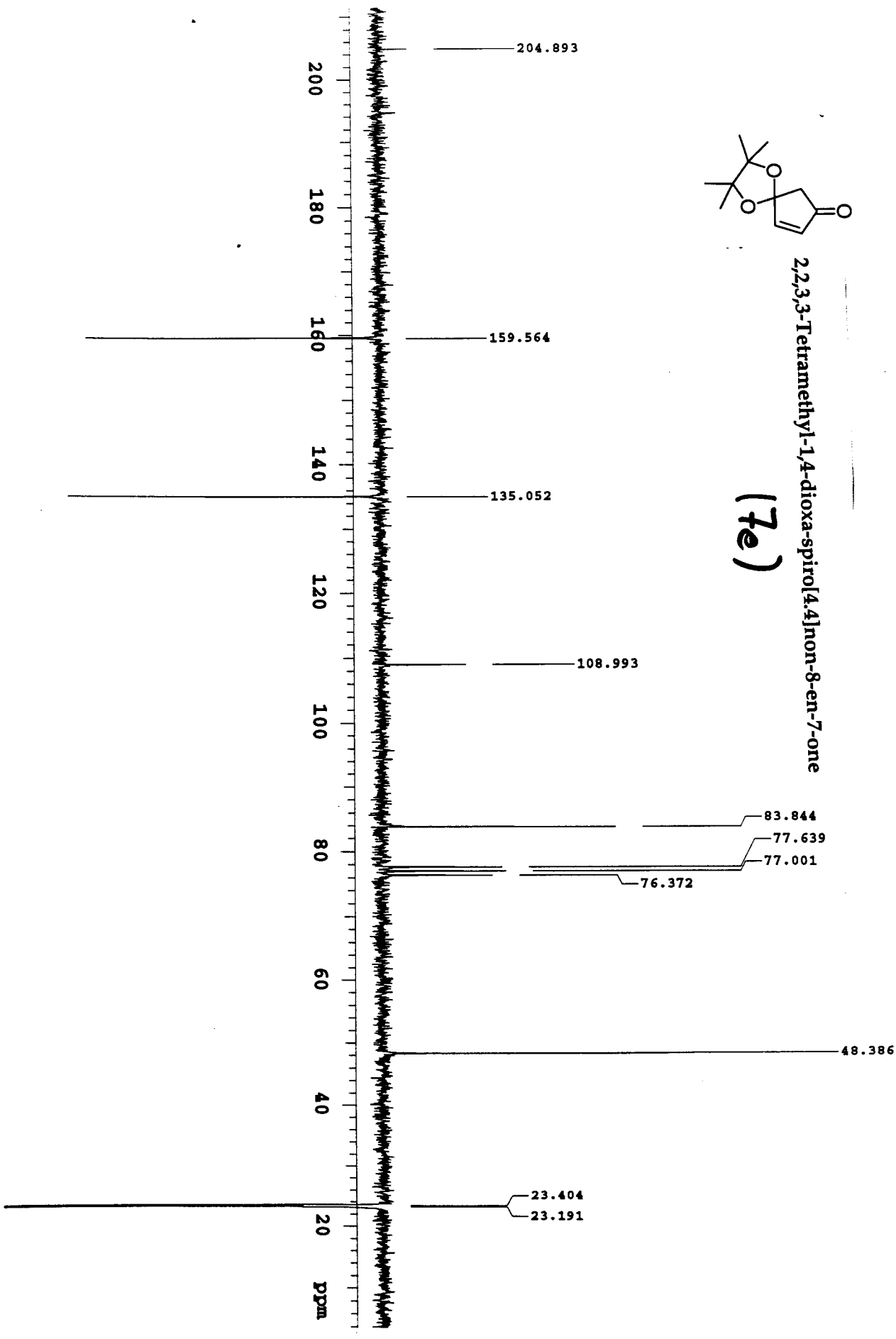
3	10819.694	143.436	18.6
4	10803.824	143.225	23.3
5	10193.435	135.133	40.4
6	9684.371	128.385	120.9
7	9669.722	128.190	107.6
8	9623.332	127.576	118.5
9	9557.410	126.702	126.0
10	9554.969	126.669	66.9
11	9534.216	126.394	50.1
12	7848.322	104.044	24.2
13	5840.142	77.422	5.6
14	5808.402	77.001	5.3
15	5775.441	76.564	5.5
16	5298.117	70.237	89.1
17	3348.535	44.391	22.4
18	3319.237	44.003	39.0

8,8,diphenyl-6,10-dioxa-spiro [4.5]dec-3-en-2-one (7d)



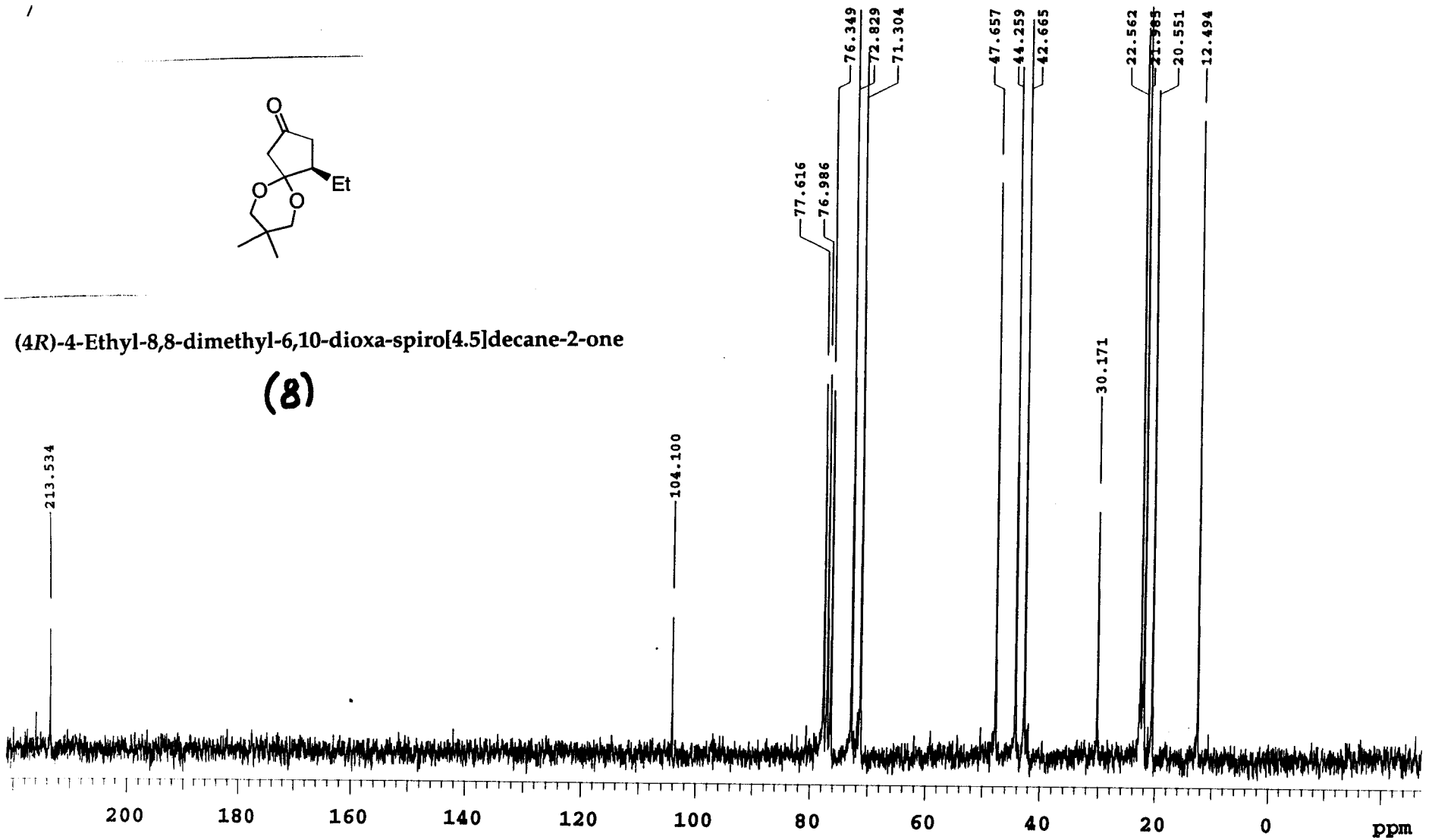


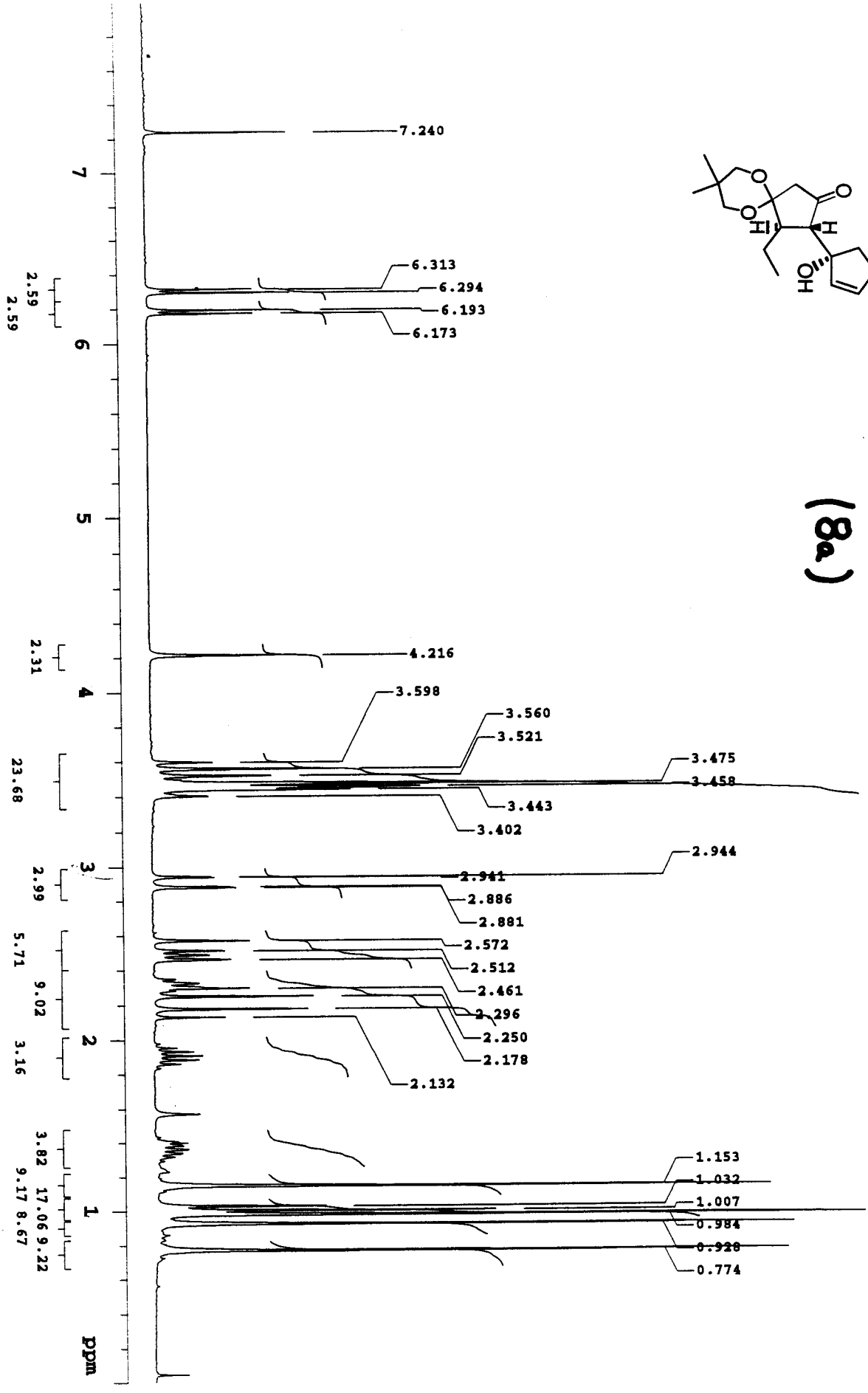
2,2,3,3-Tetramethyl-1,4-dioxa-spiro[4.4]non-8-en-7-one

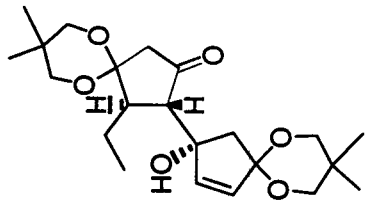
(7e)

(4*R*)-4-Ethyl-8,8-dimethyl-6,10-dioxa-spiro[4.5]decane-2-one

(8)

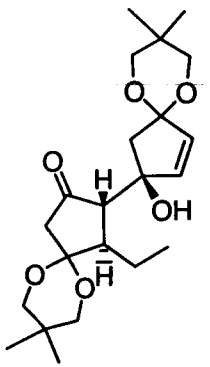






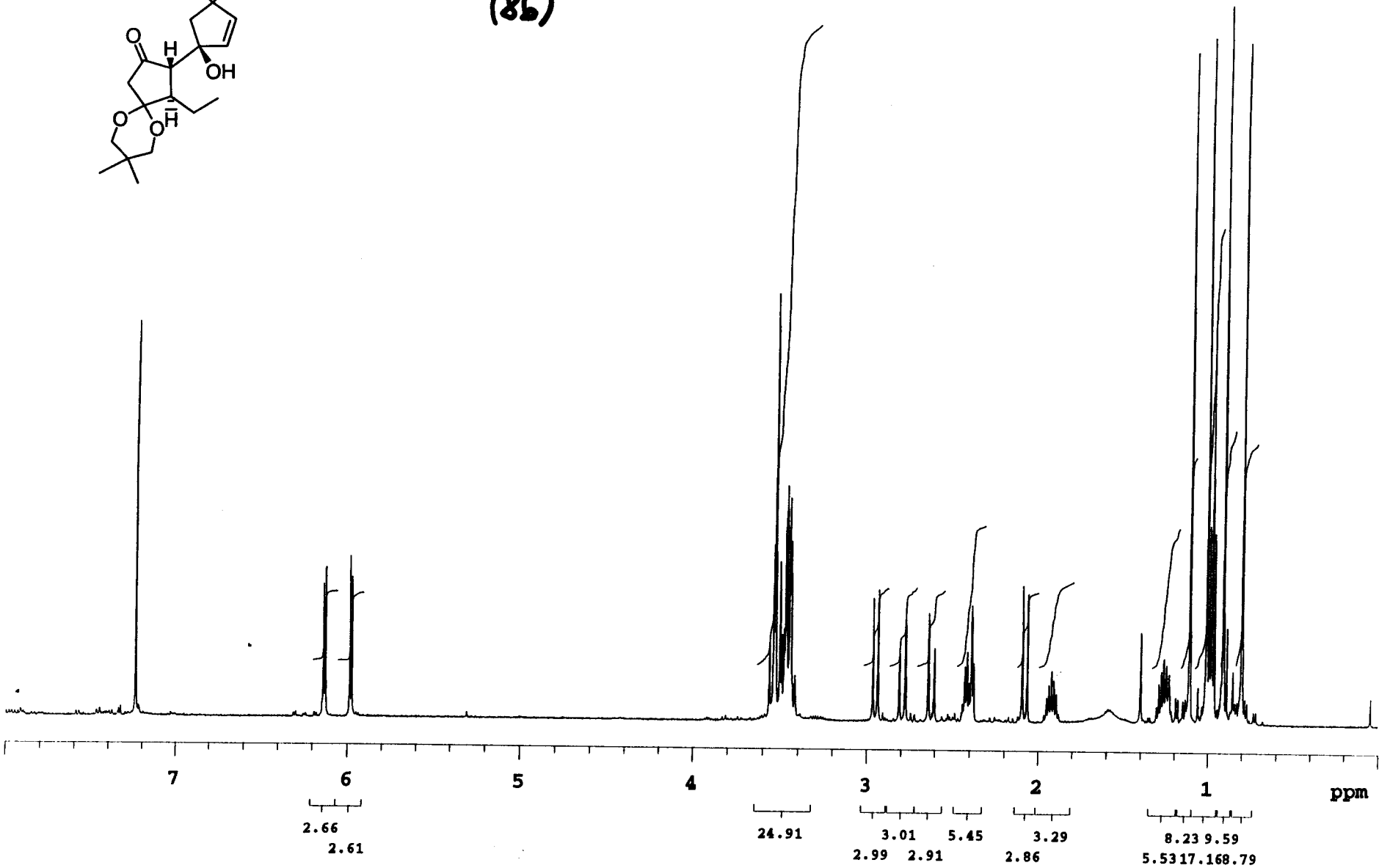
(8a)

4-Ethyl-3-(2-hydroxy-8,8-dimethyl-6,10-dioxaspiro[4.5]dec-3-en-2-yl)-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one



4-Ethyl-3-(2-hydroxy-8,8-dimethyl-6,10-dioxaspiro[4.5]dec-3-en-2-yl)-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one

(8b)



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5	6459.985	128.467	109.2
6	6442.437	128.118	107.5
7	6382.926	126.935	63.7
8	6358.511	126.449	103.5
9	6351.263	126.305	61.7
10	5262.897	104.661	36.2
11	3903.679	77.631	53.9
12	3872.016	77.001	53.4
13	3839.971	76.364	54.3
14	3555.386	70.705	51.9
15	3460.779	68.823	51.6
16	2389.198	47.513	62.9
17	2252.627	44.797	42.4
18	2249.957	44.744	63.6
19	2153.824	42.832	64.7
20	1035.320	20.589	65.0
21	622.939	12.388	62.6

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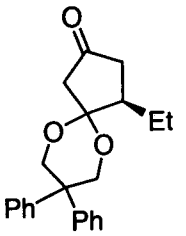
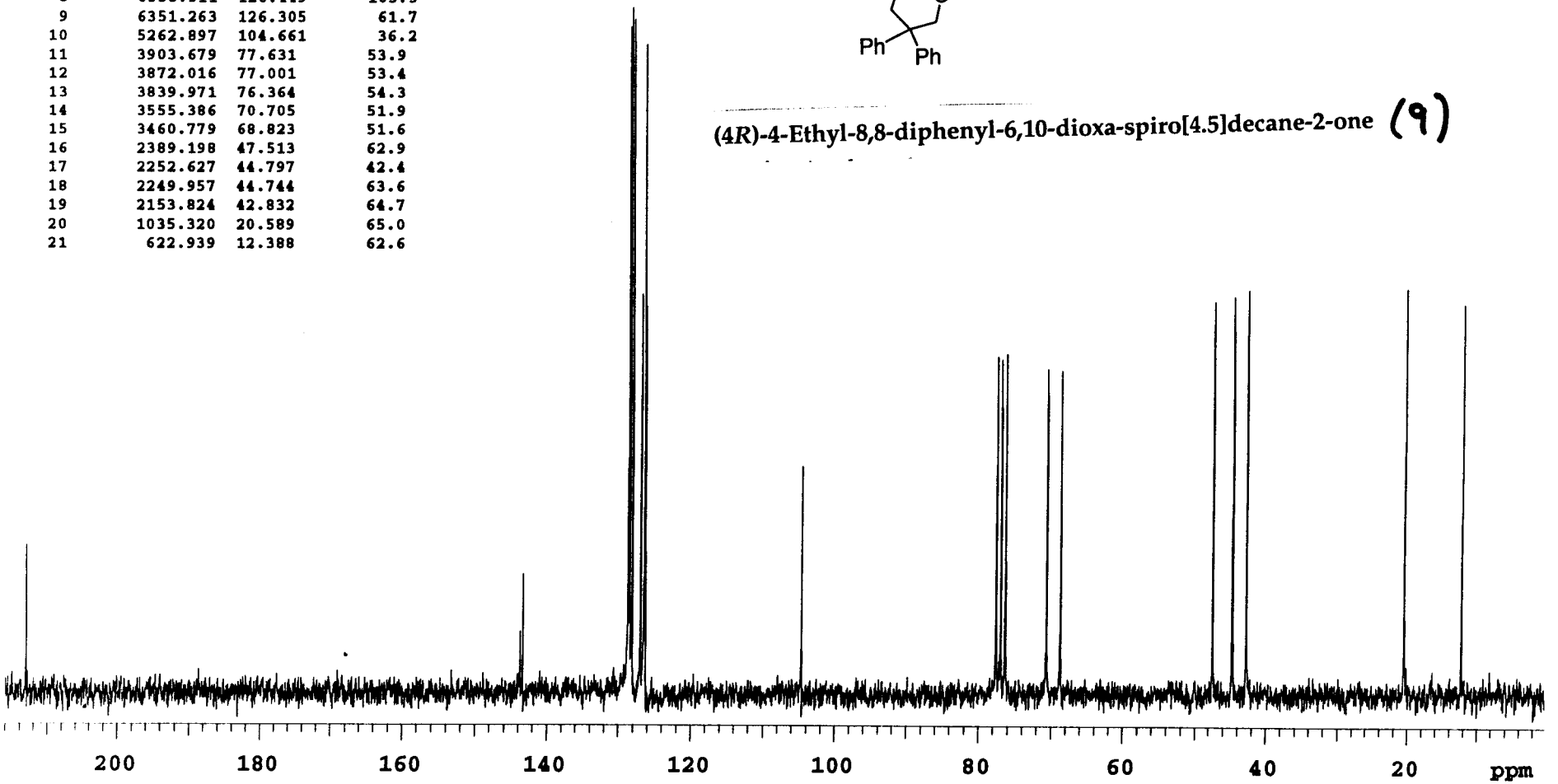
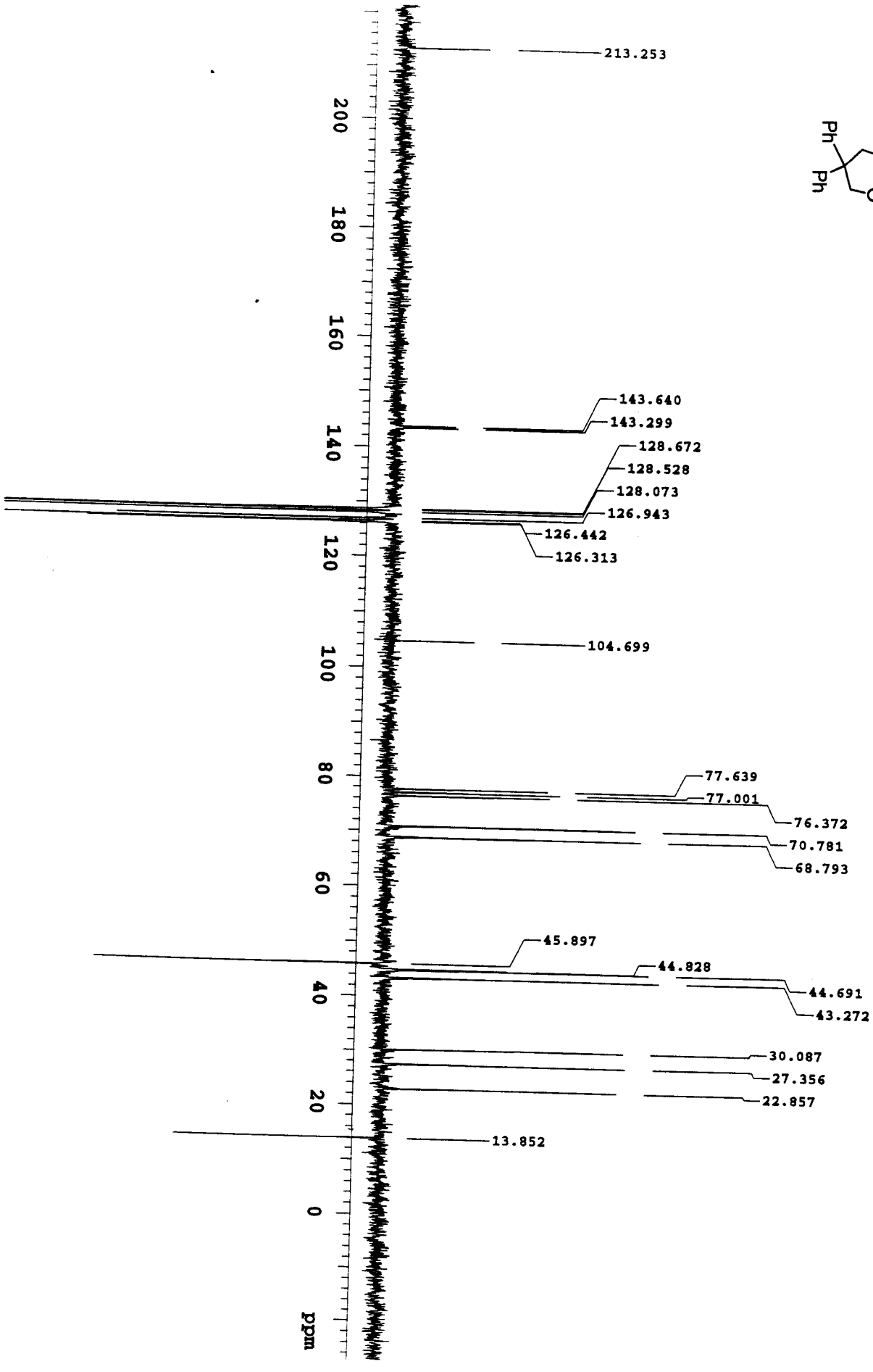
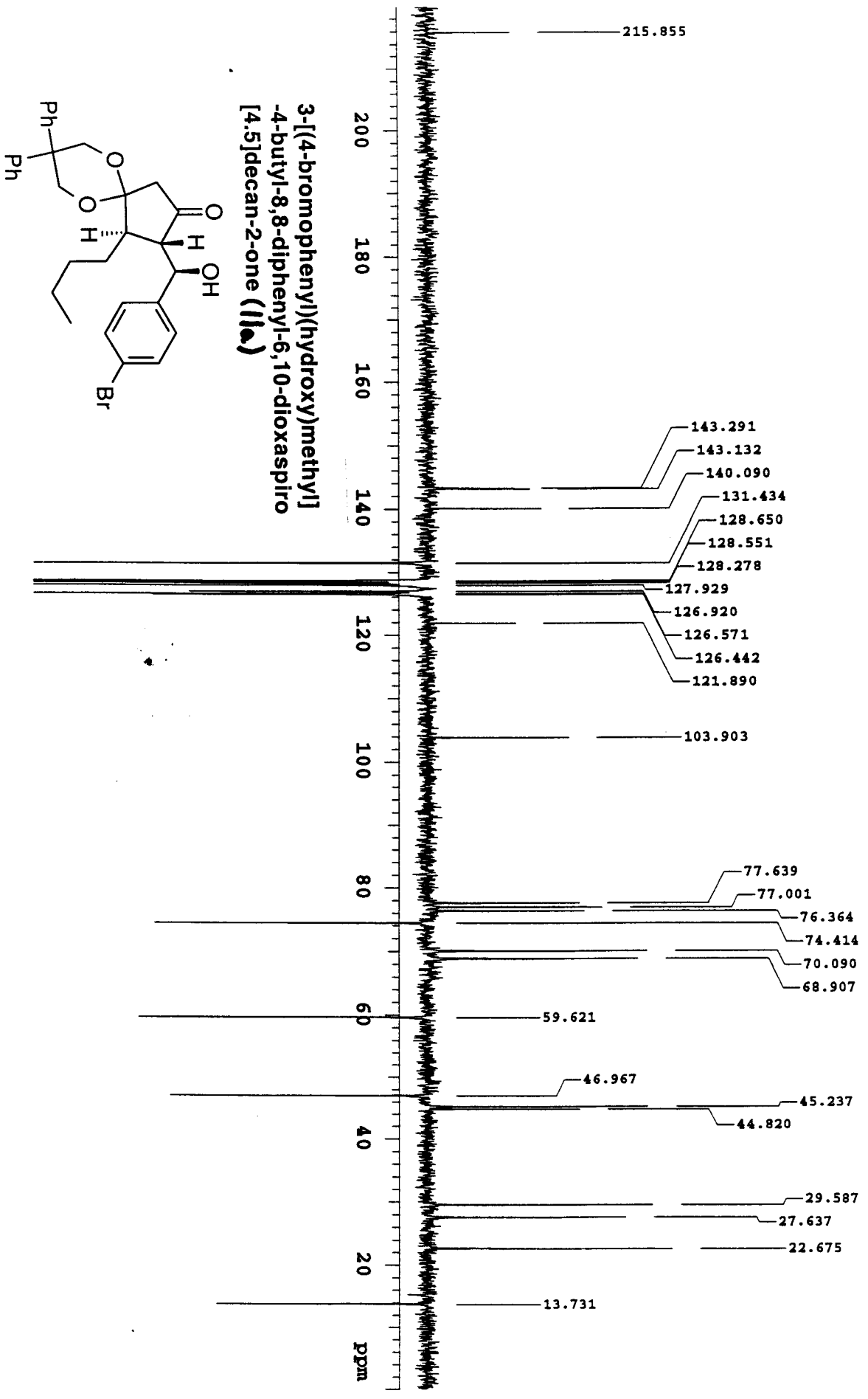


(4*R*)-4-Ethyl-8,8-diphenyl-6,10-dioxa-spiro[4.5]decane-2-one (9)





(4*R*)-4-Butyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (10)


3-[(4-bromophenyl)(hydroxy)methyl]
-4-butyl-8,8-diphenyl-6,10-dioxaspiro
[4.5]decan-2-one (11a)
Ph
Ph
O
O
H
O
H
OH
Br
215.855
143.291
143.132
140.090
131.434
128.650
128.551
128.278
127.929
126.920
126.571
126.442
121.890
103.903
77.639
77.001
76.364
74.414
70.090
68.907
59.621
46.967
45.237
44.820
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27.637
22.675
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140
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80
60
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20
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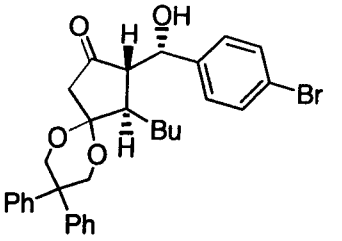
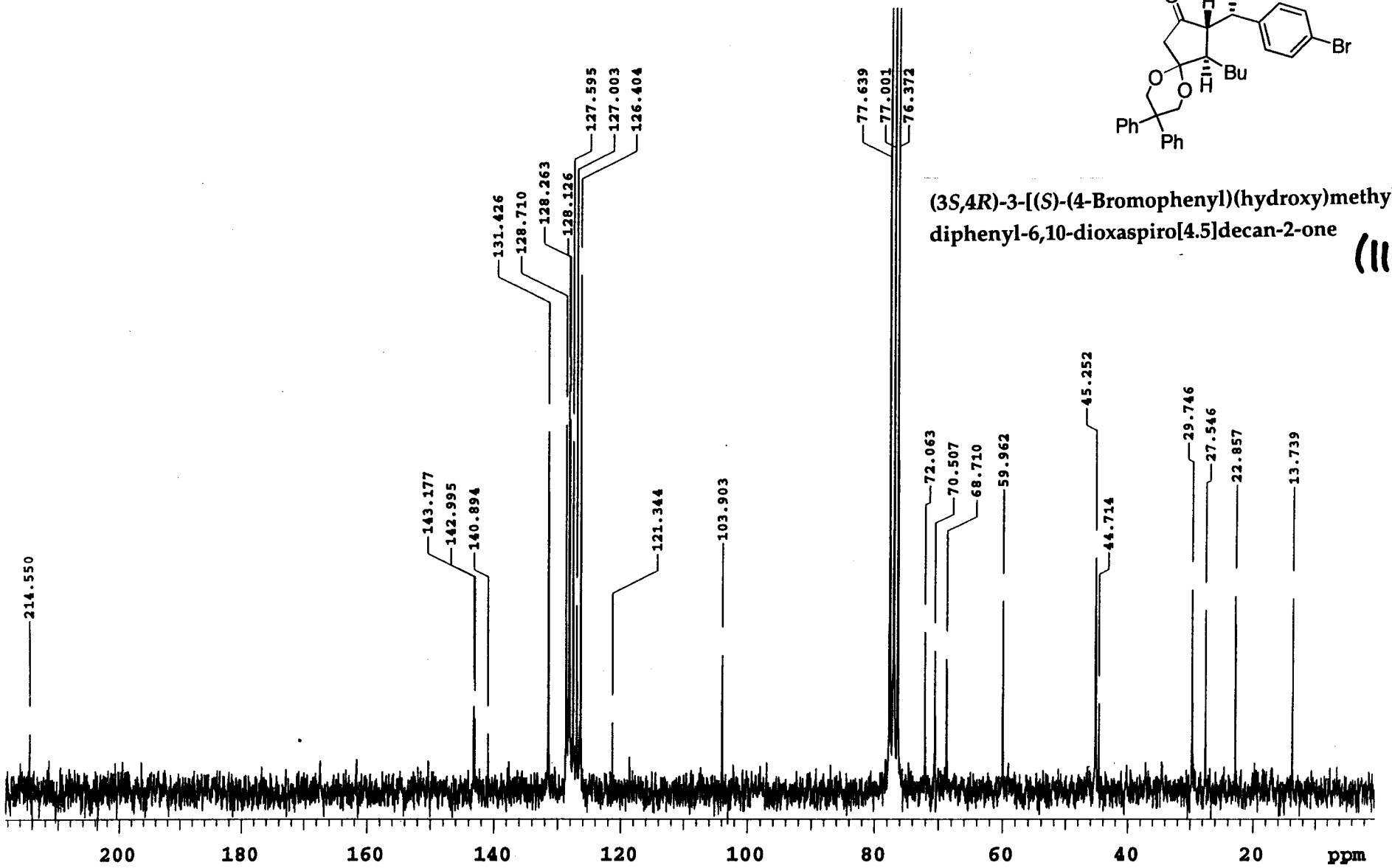
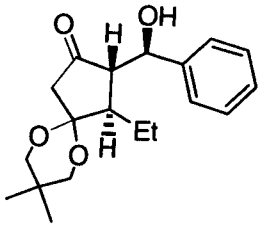


(3*S*,4*R*)-3-[(*S*)-(4-Bromophenyl)(hydroxy)methyl]-4-butyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one

(11b)





(3*S*,4*R*)-4-Ethyl-3-[(*R*)-hydroxy(phenyl)methyl]-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one

(13a)

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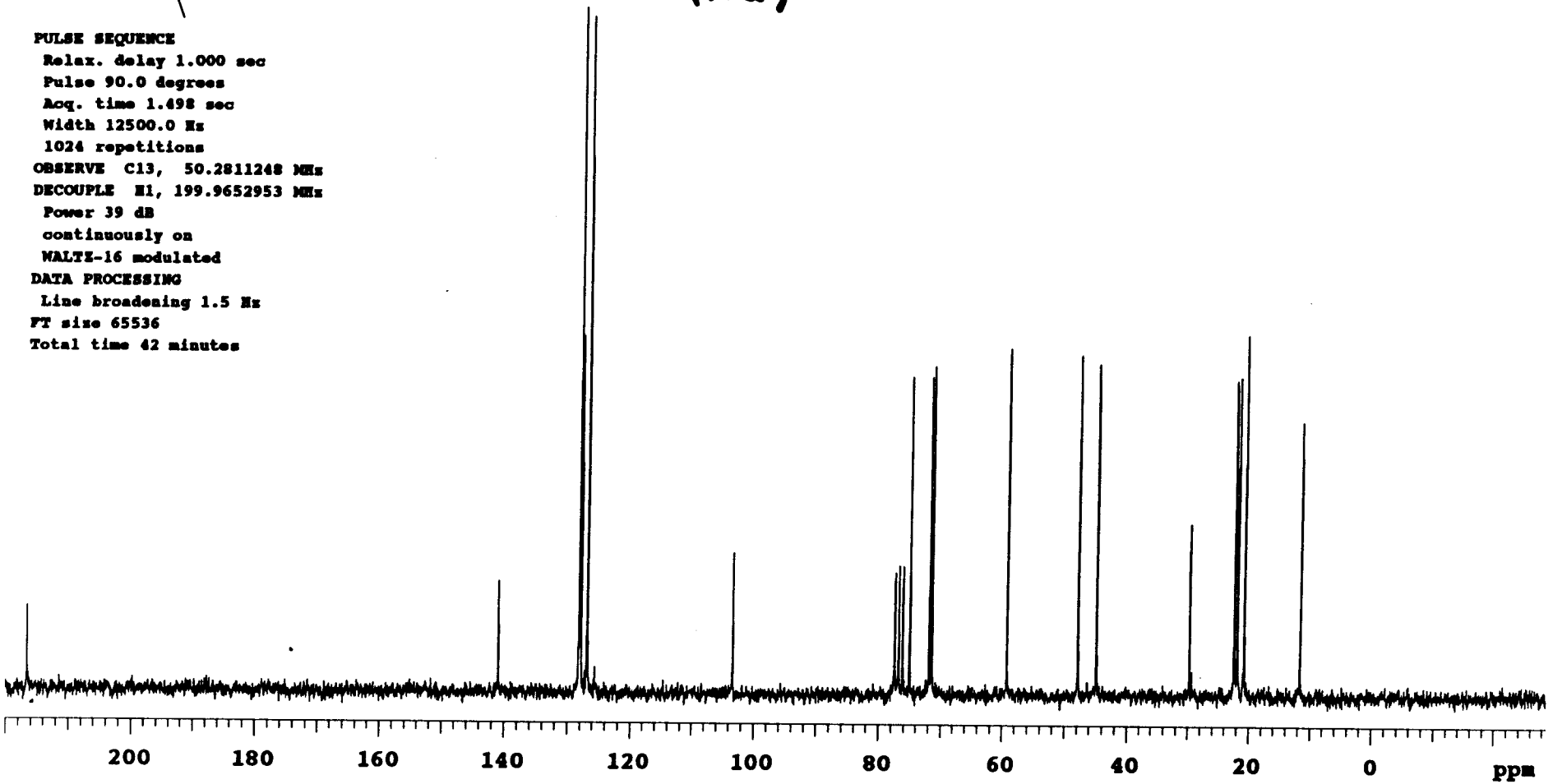
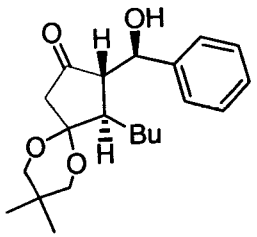
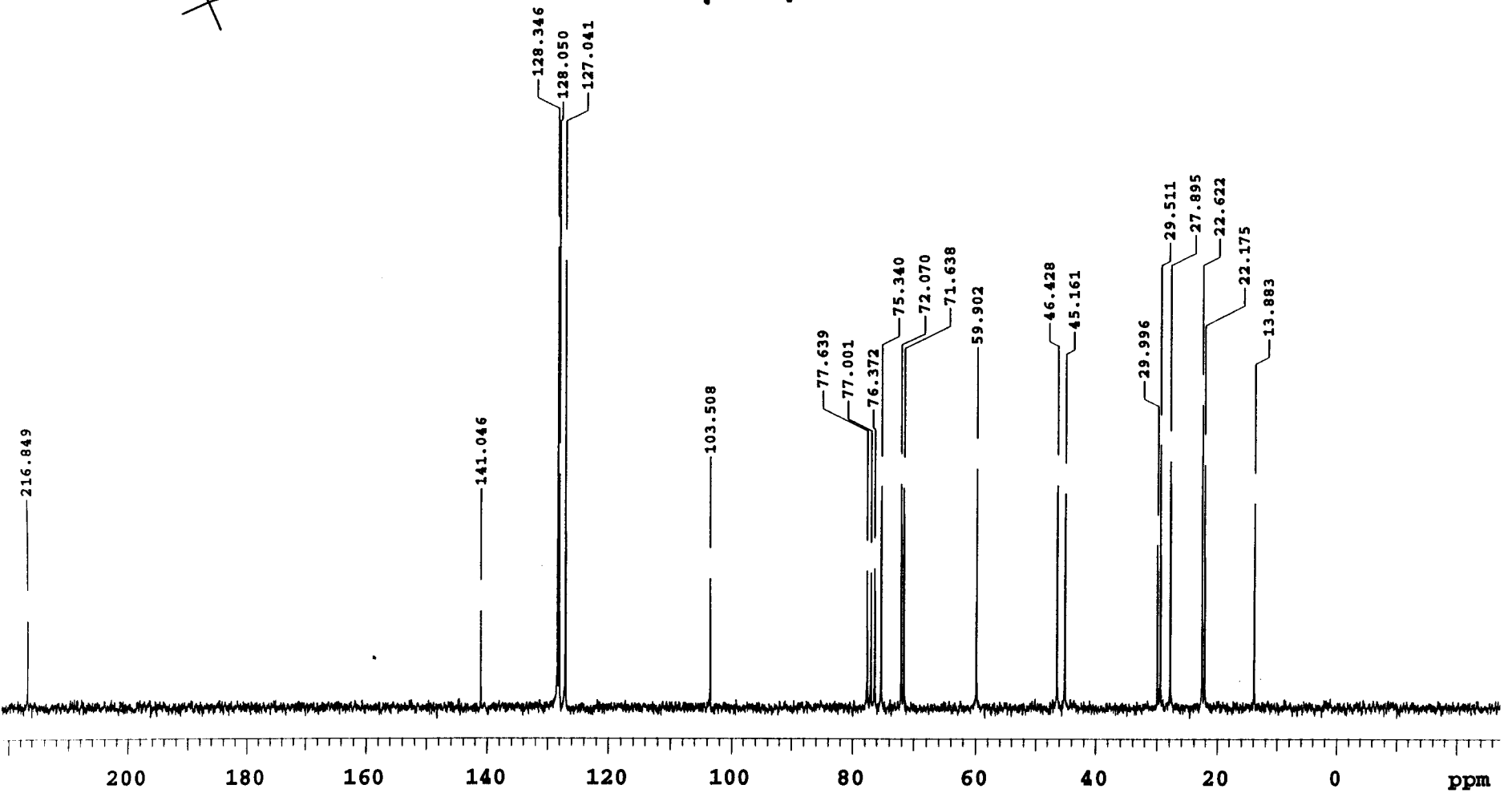
Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 1.498 sec
Width 12500.0 Hz
1024 repetitions
OBSERVE C13, 50.2811248 MHz
DECOUPLE H1, 199.9652953 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.5 Hz
FT size 65536
Total time 42 minutes





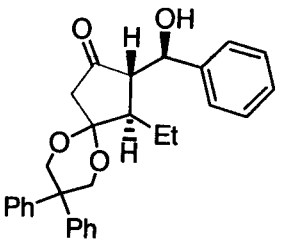
(3*S*,4*R*)-4-Butyl-3-[(*R*)-hydroxy(phenyl)methyl]-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one

(14a)



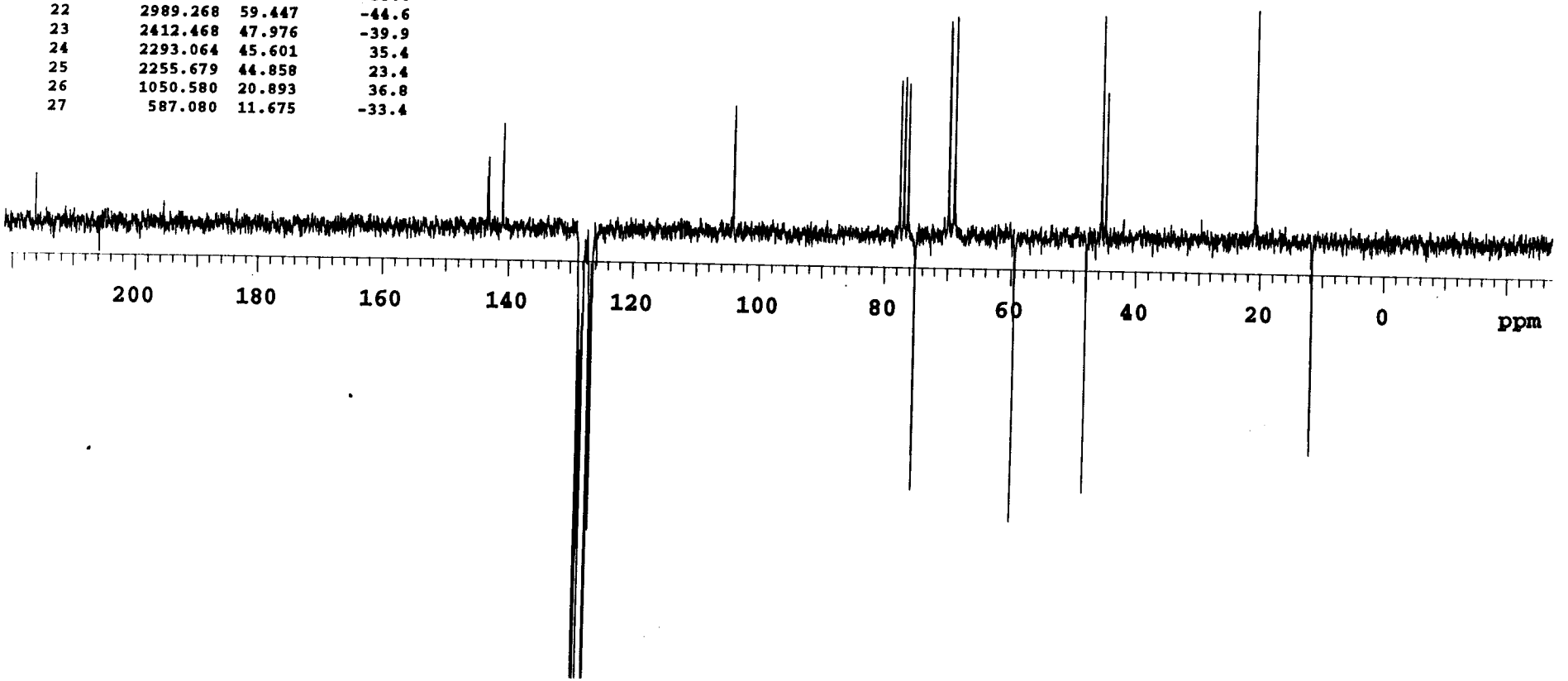
INDEX	FREQUENCY	PPM	HEIGHT
1	10869.147	216.151	7.9
2	10348.044	205.788	-4.5
3	7214.174	143.466	8.2
4	7205.019	143.284	11.3
5	7089.430	140.985	16.8
6	6467.234	128.612	-79.0
7	6453.882	128.346	-94.5
8	6450.448	128.278	-88.6
9	6439.385	128.058	-48.2
10	6431.756	127.906	-80.5
11	6382.163	126.920	-92.9
12	6372.626	126.730	-81.9
13	6358.893	126.457	-47.1
14	6325.704	125.797	-5.7
15	5237.338	104.153	20.2
16	3904.060	77.639	24.8
17	3872.016	77.001	25.3
18	3840.353	76.372	24.3
19	3778.934	75.150	-39.9
20	3516.475	69.931	34.2
21	3471.842	69.043	35.0
22	2989.268	59.447	-44.6
23	2412.468	47.976	-39.9
24	2293.064	45.601	35.4
25	2255.679	44.858	23.4
26	1050.580	20.893	36.8
27	587.080	11.675	-33.4

/export/home/vnmr1/vnmrsys/data/auto/we/0202



(3*S*,4*R*)-4-Ethyl-3-[(*R*)-hydroxy(phenyl)methyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one

(15a)



INDEX	FREQUENCY	PPM	HEIGHT
1	10877.540	216.318	19.9
2	10865.332	216.075	-5.2
3	7209.596	143.375	18.3
4	7202.730	143.238	16.7
5	7087.522	140.947	22.3
6	6529.796	129.856	-4.3
7	6468.378	128.634	73.2
8	6455.408	128.376	88.1
9	6450.448	128.278	92.7
10	6440.911	128.088	49.1
11	6432.900	127.929	83.3
12	6381.019	126.897	126.0
13	6368.430	126.647	81.1
14	6356.985	126.419	48.6
15	5231.615	104.039	17.9
16	3903.679	77.631	51.6
17	3871.634	76.994	49.9
18	3839.971	76.364	50.8
19	3781.605	75.203	38.3
20	3525.249	70.105	32.4
21	3463.449	68.876	33.7
22	3006.816	59.795	42.7
23	2356.009	46.853	43.0
24	2284.290	45.427	36.3
25	2254.916	44.843	17.0
26	1487.757	29.587	48.7
27	1390.861	27.660	40.4
28	1140.609	22.683	48.6
29	692.750	13.776	40.5

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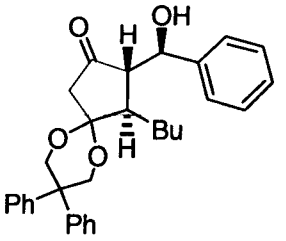
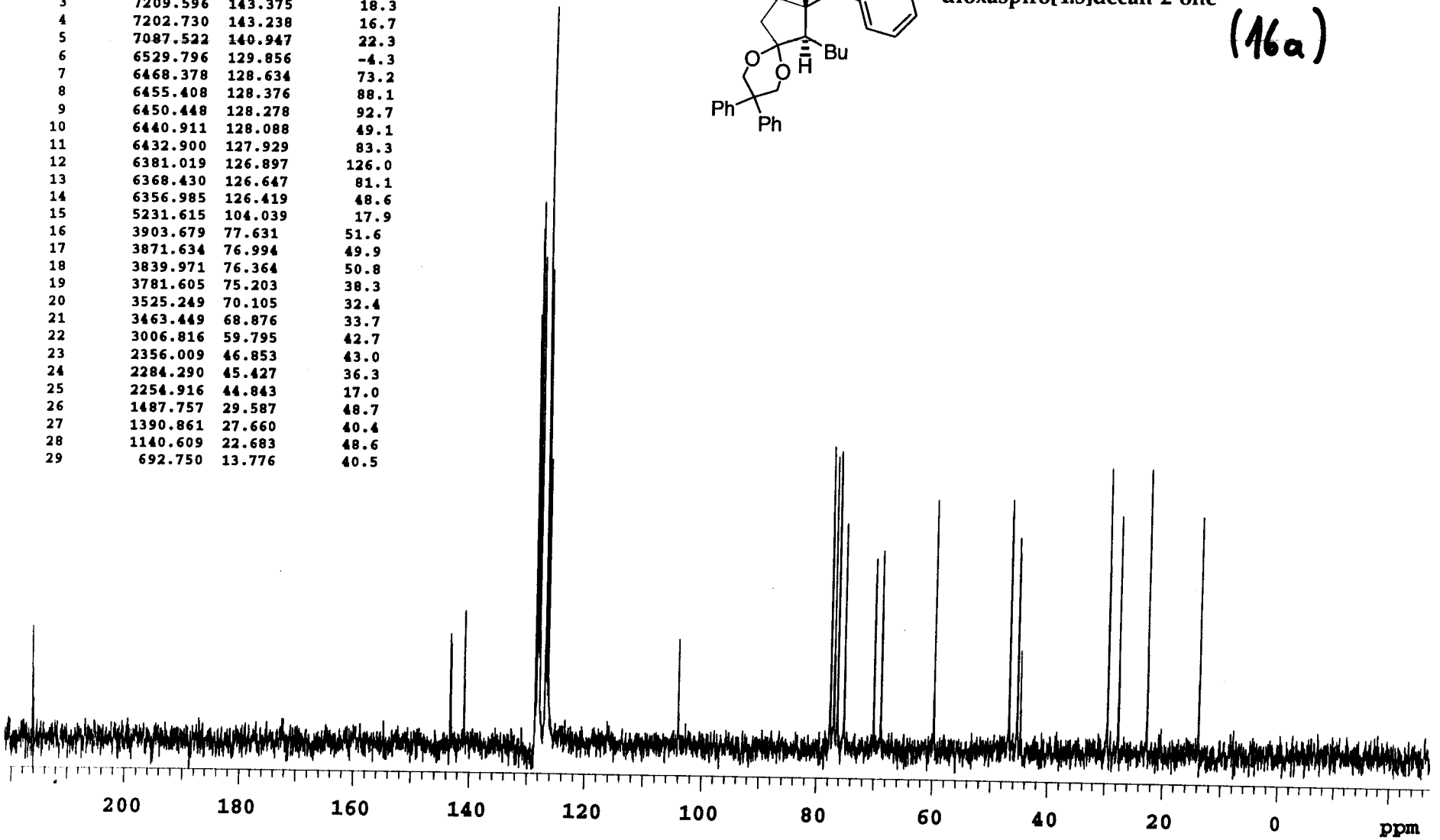
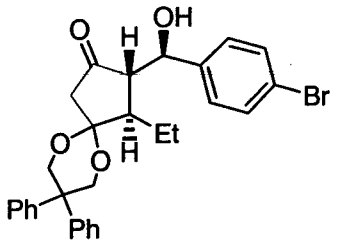


(3*S*,4*R*)-4-Butyl-3-[(*R*)-hydroxy(phenyl)methyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one

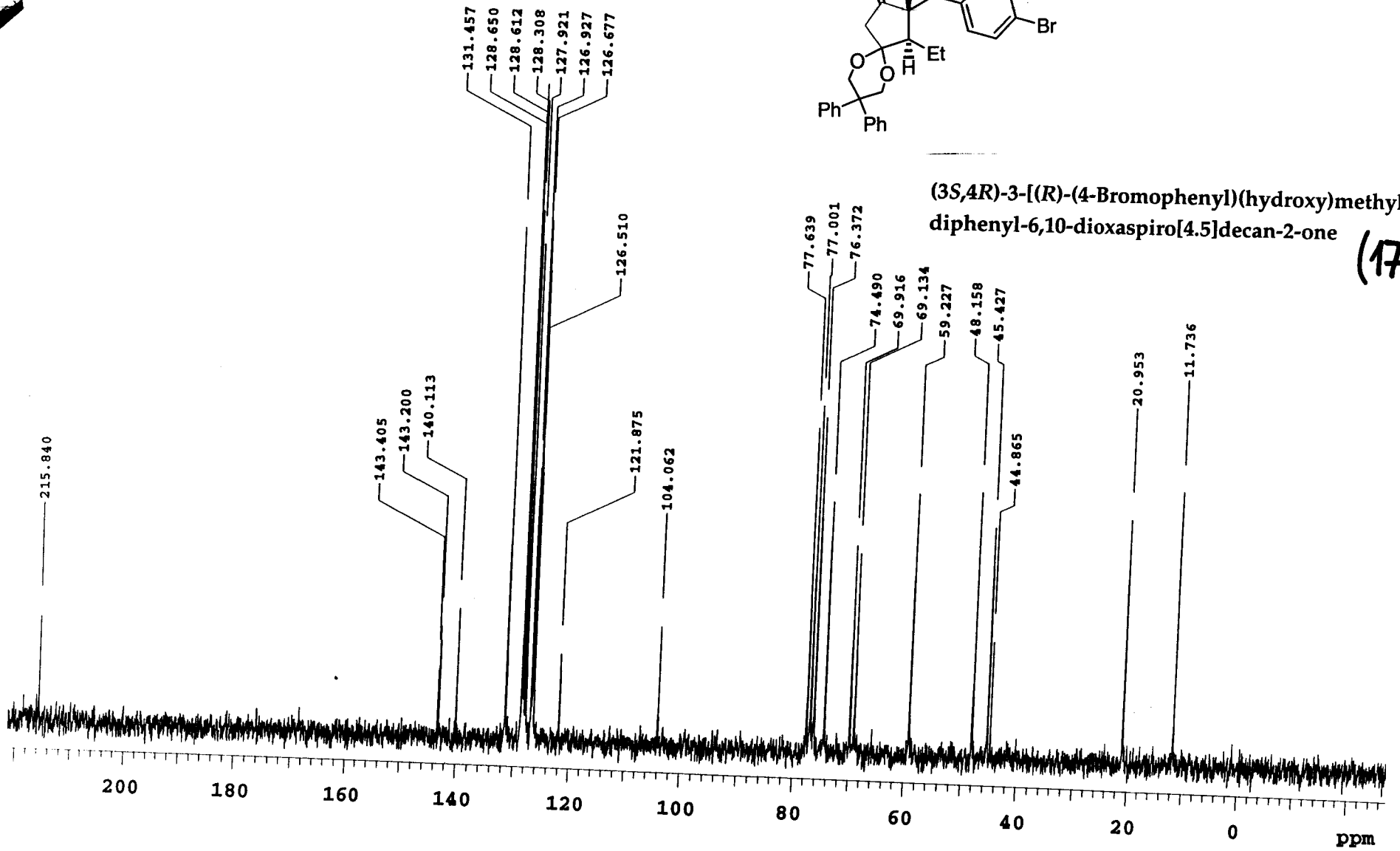
(16a)

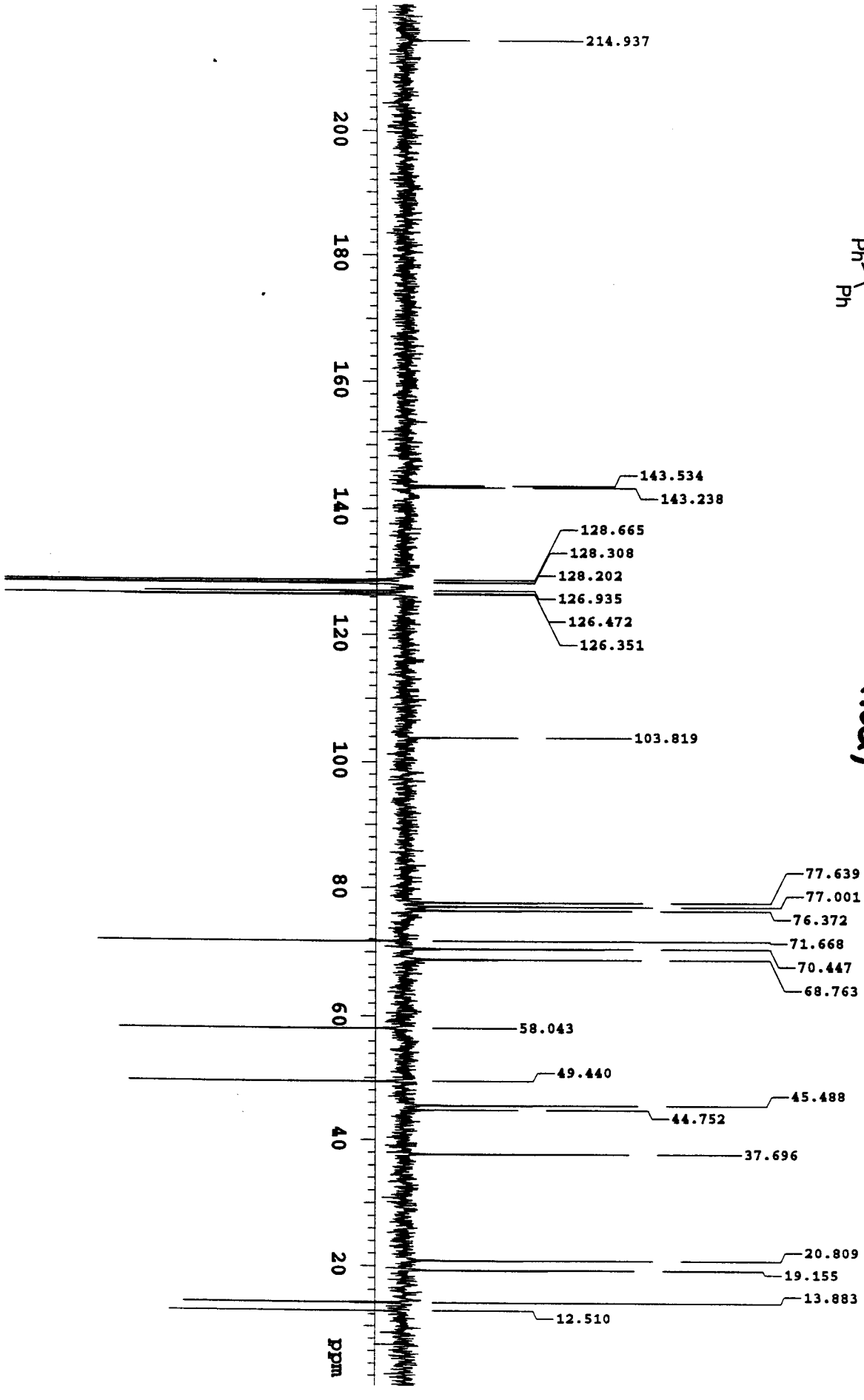
S 30

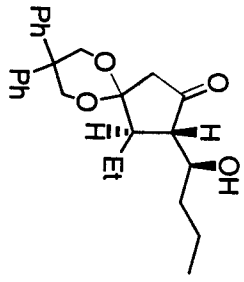




(3*S*,4*R*)-3-[(*R*)-(4-Bromophenyl)(hydroxy)methyl]-4-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (17a)

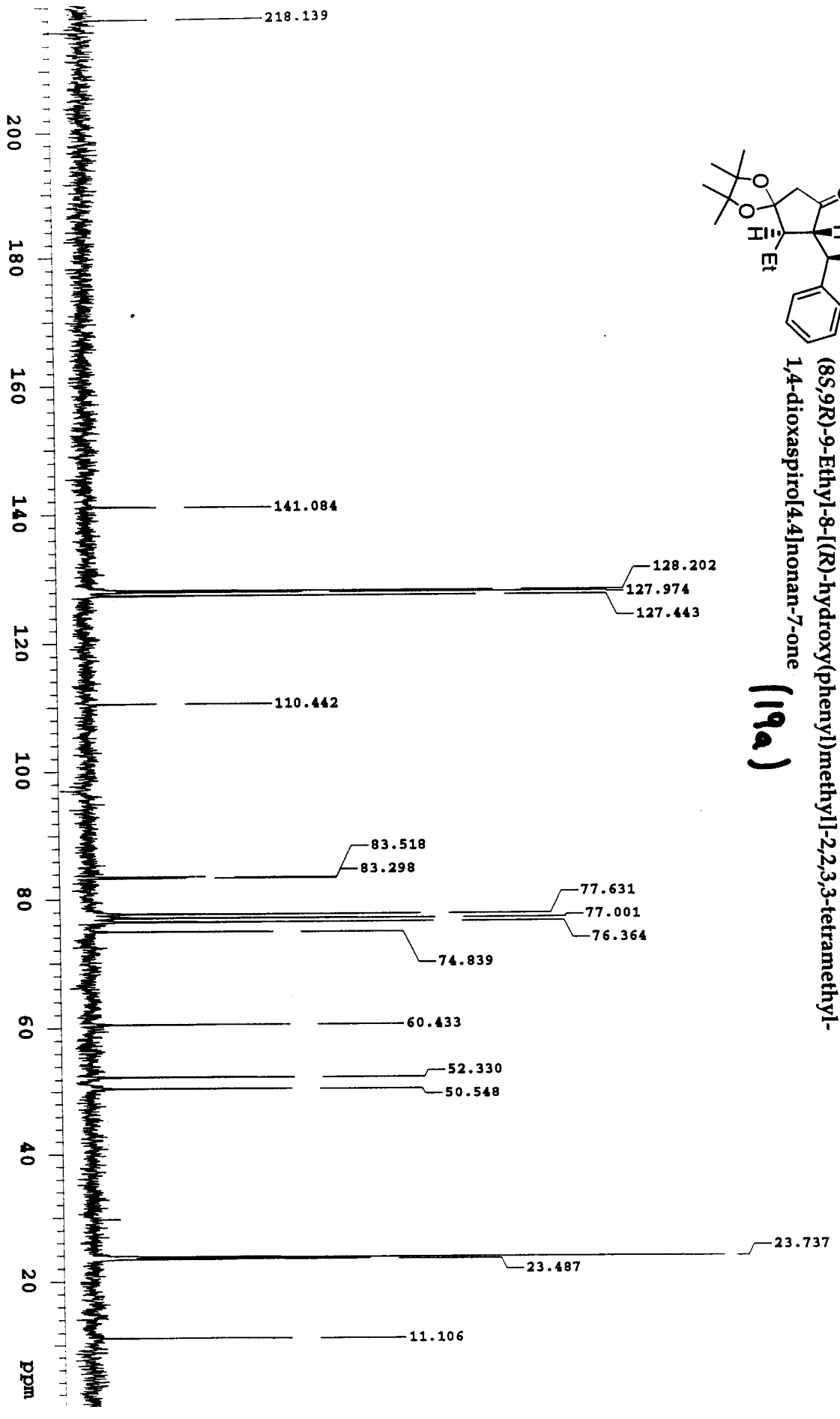


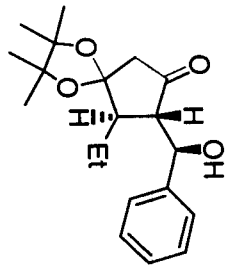




(3*S*,4*R*)-4-Ethyl-3-[(1*S*)-1-hydroxybutyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one

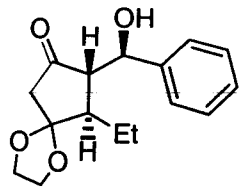
(18a)





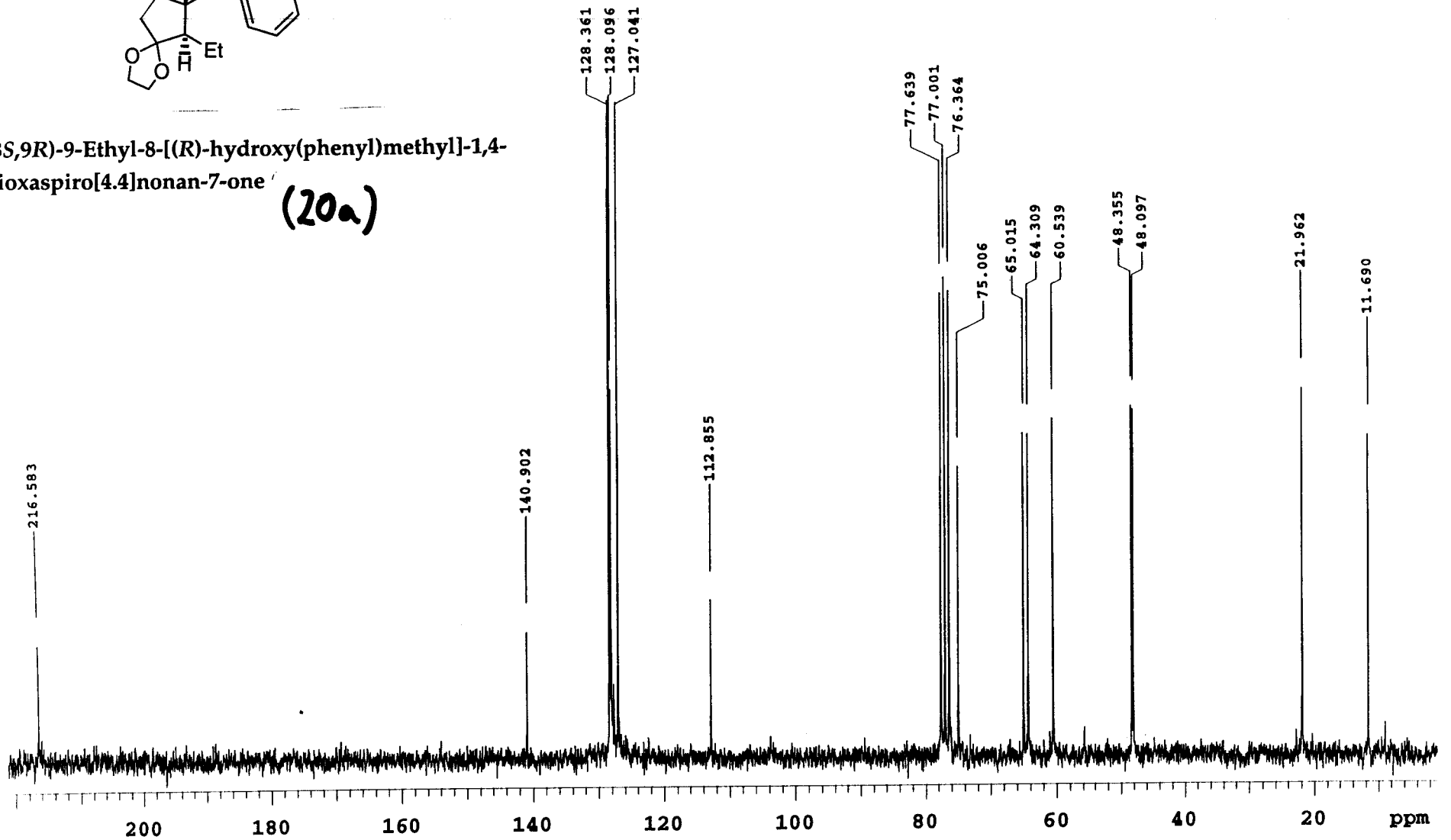
(8*S*,9*R*)-9-Ethyl-8-[(*R*)-hydroxy(phenyl)methyl]-2,2,3,3-tetramethyl-1,4-dioxaspiro[4.4]nonan-7-one

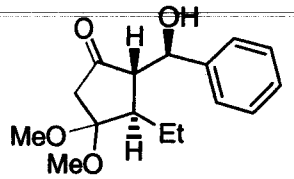
(19a)



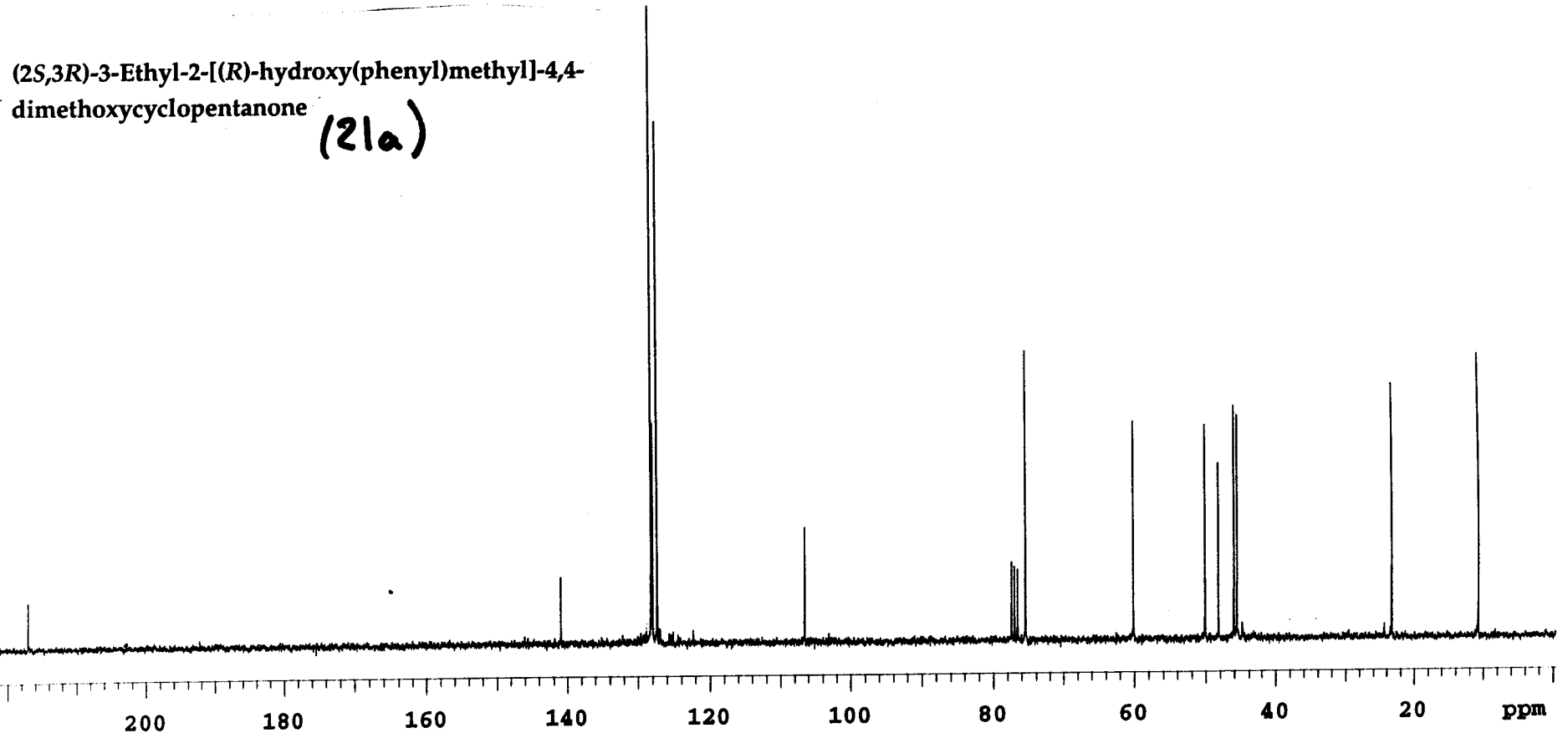
(8*S*,9*R*)-9-Ethyl-8-[(*R*)-hydroxy(phenyl)methyl]-1,4-dioxaspiro[4.4]nonan-7-one

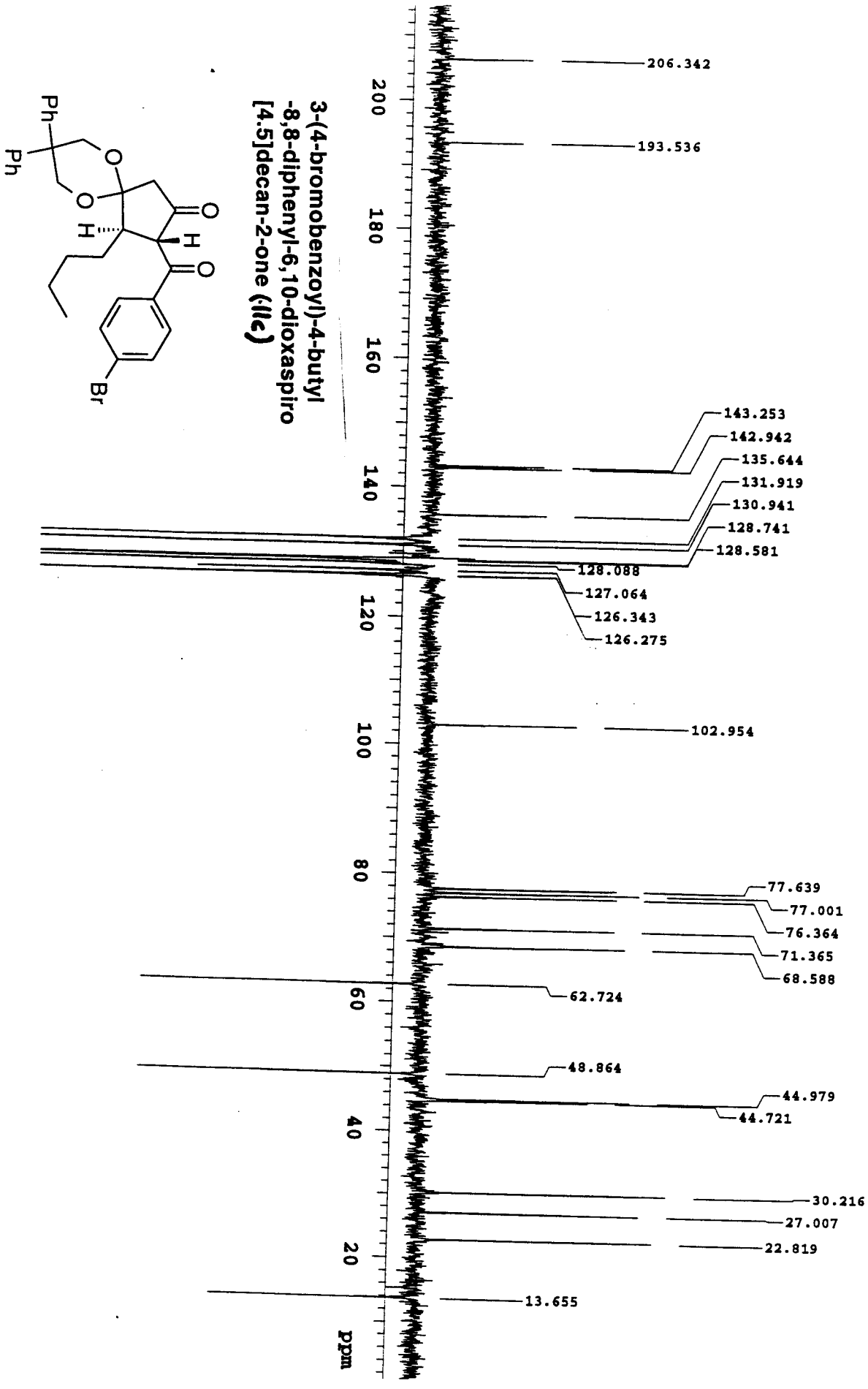
(20a)





(2*S*,3*R*)-3-Ethyl-2-[(*R*)-hydroxy(phenyl)methyl]-4,4-dimethoxycyclopentanone (21a)

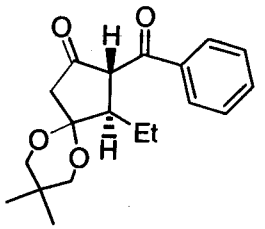



3-(4-bromobenzoyl)-4-butyl
-8,8-diphenyl-6,10-dioxaspiro
[4.5]decan-2-one (IIc)
Ph
Ph
O
O
H
O
H
O
Br
206.342
193.536
143.253
142.942
135.644
131.919
130.941
128.741
128.581
128.088
127.064
126.343
126.275
102.954
77.639
77.001
76.364
71.365
68.588
62.724
48.864
44.979
44.721
30.216
27.007
22.819
13.655
200
180
160
140
120
100
80
60
40
20
ppm

/export/home/vnmr1/vnmrsys/data/auto/th/0202

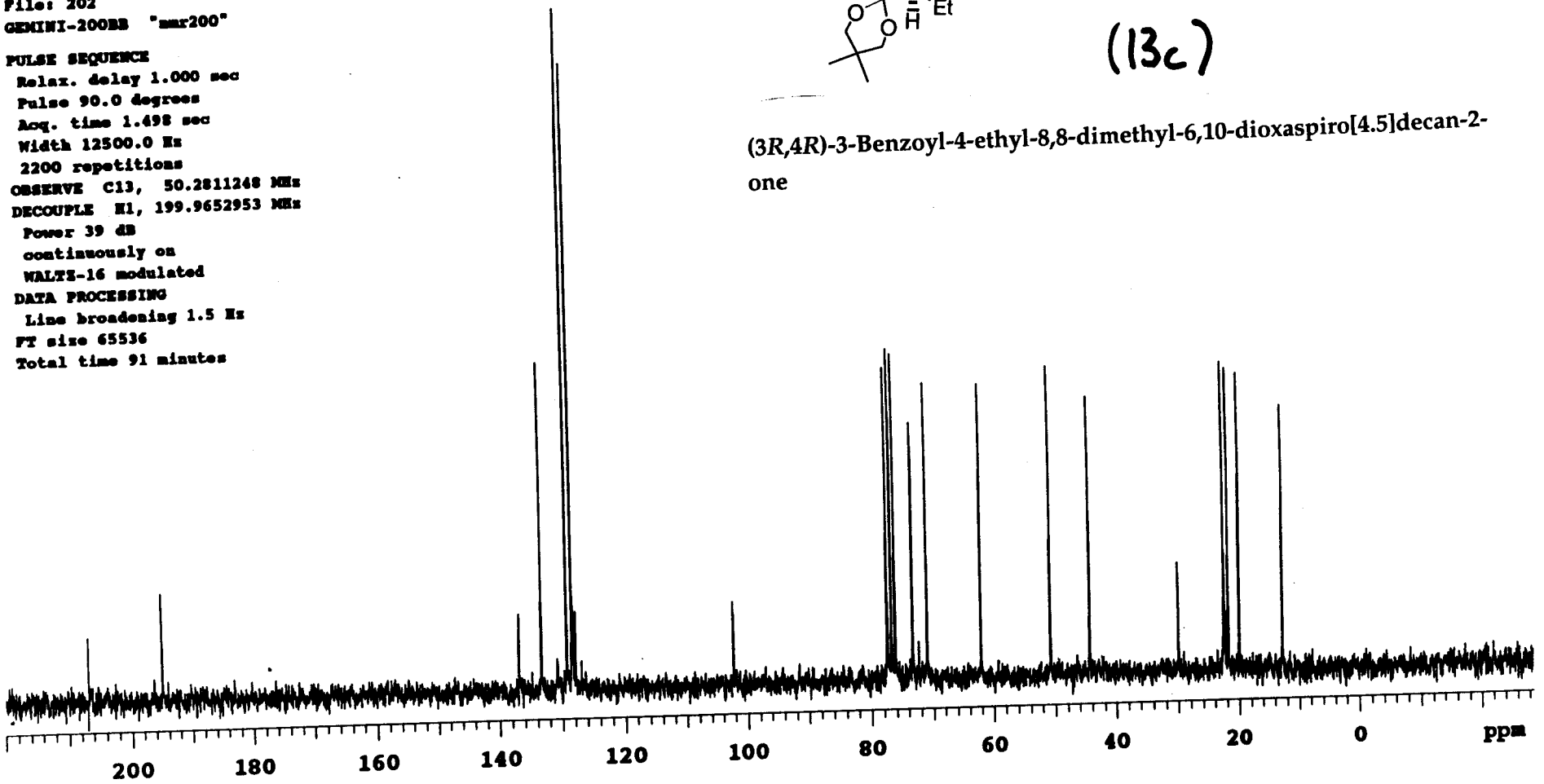
Solvent: CDCL3
Ambient temperature
Sample #2
File: 202
GEMINI-200BB "nmr200"

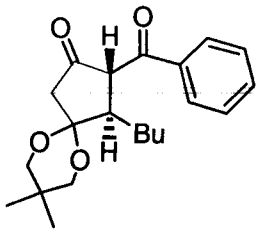
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 1.498 sec
Width 12500.0 Hz
2200 repetitions
OBSERVE C13, 50.2811248 MHz
DECOUPLE H1, 199.9652953 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.5 Hz
FT size 65536
Total time 91 minutes



(13c)

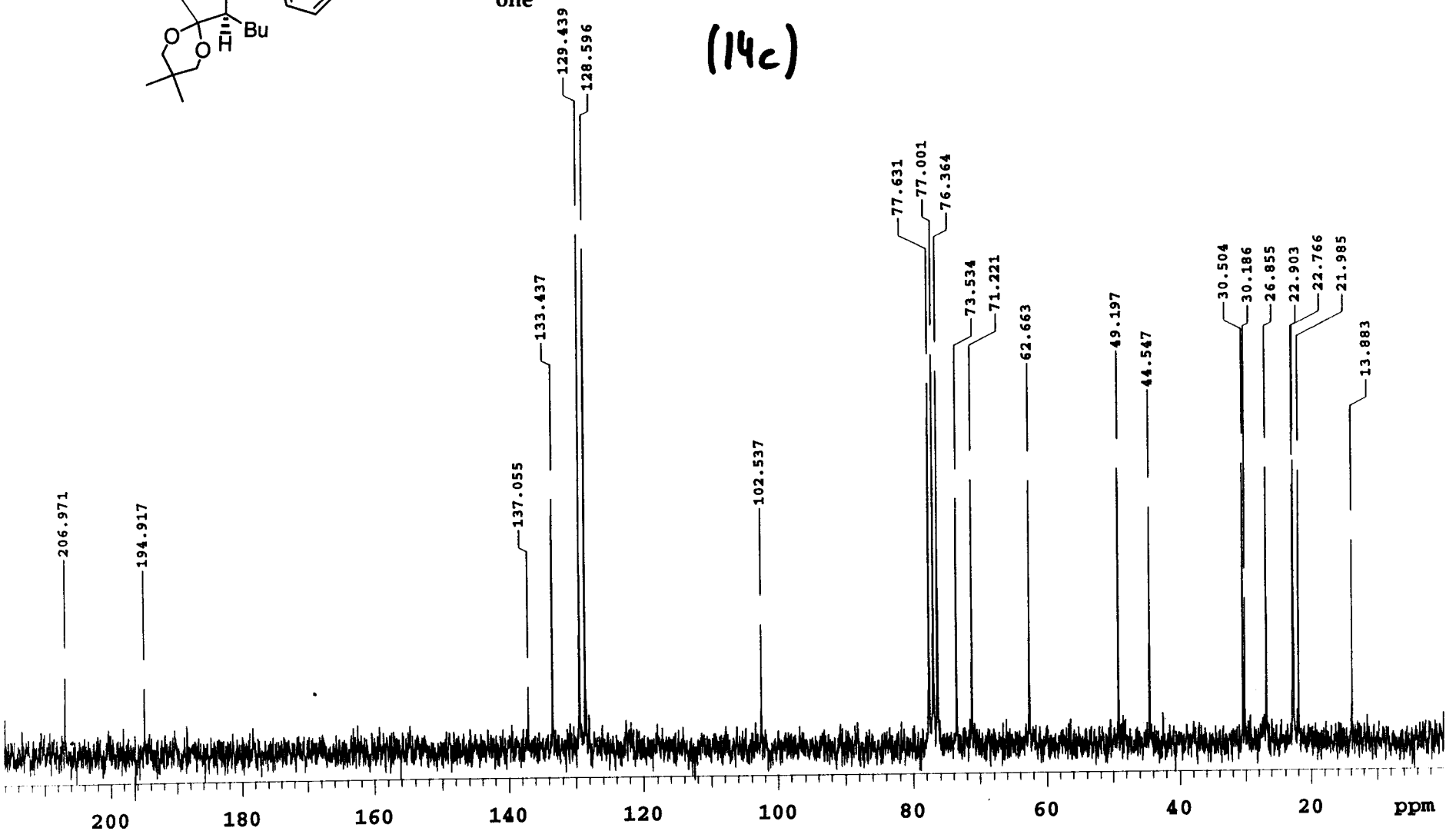
(3*R*,4*R*)-3-Benzoyl-4-ethyl-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one

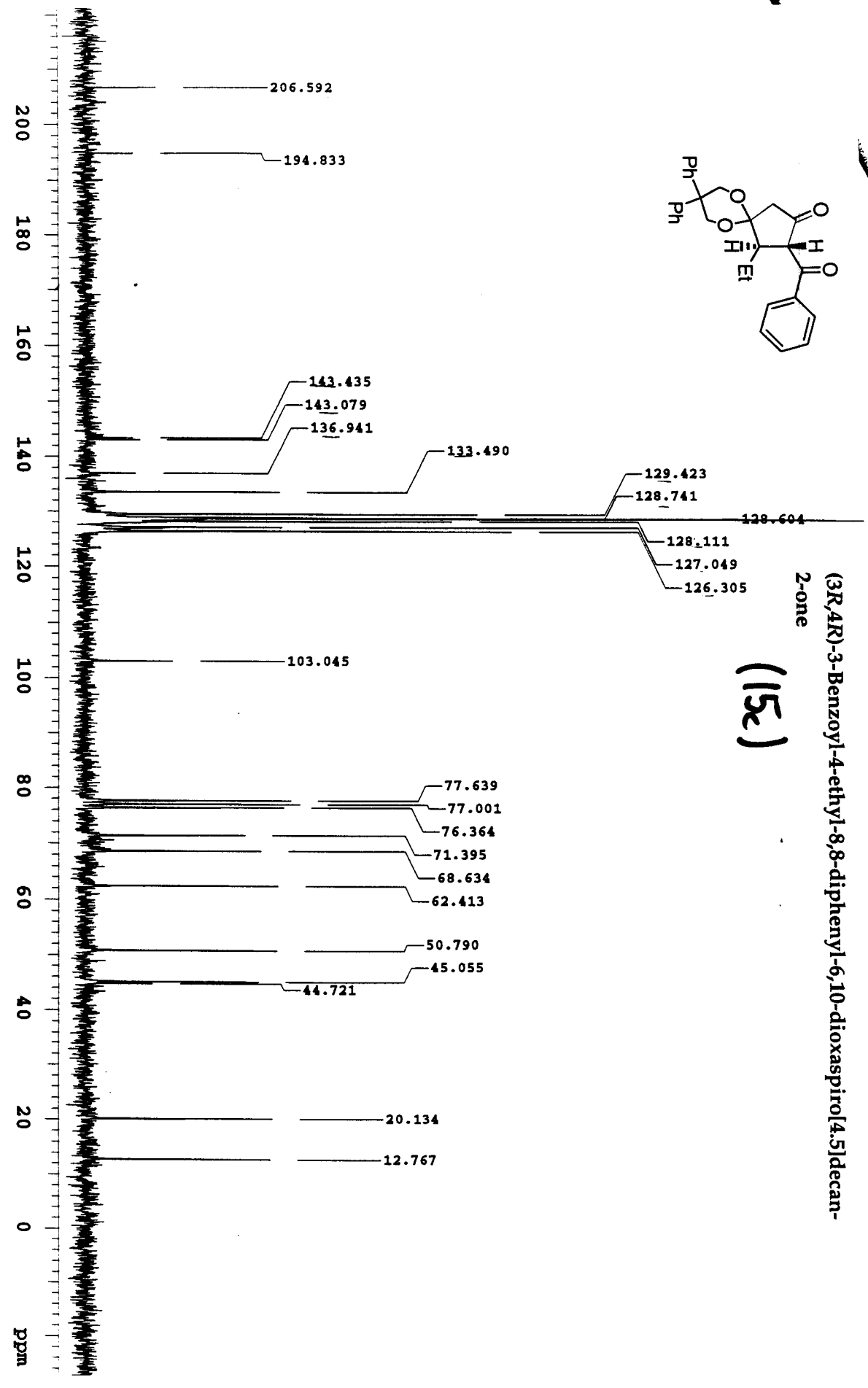




(3*R*,4*R*)-3-Benzoyl-4-butyl-8,8-dimethyl-6,10-dioxaspiro[4.5]decan-2-one

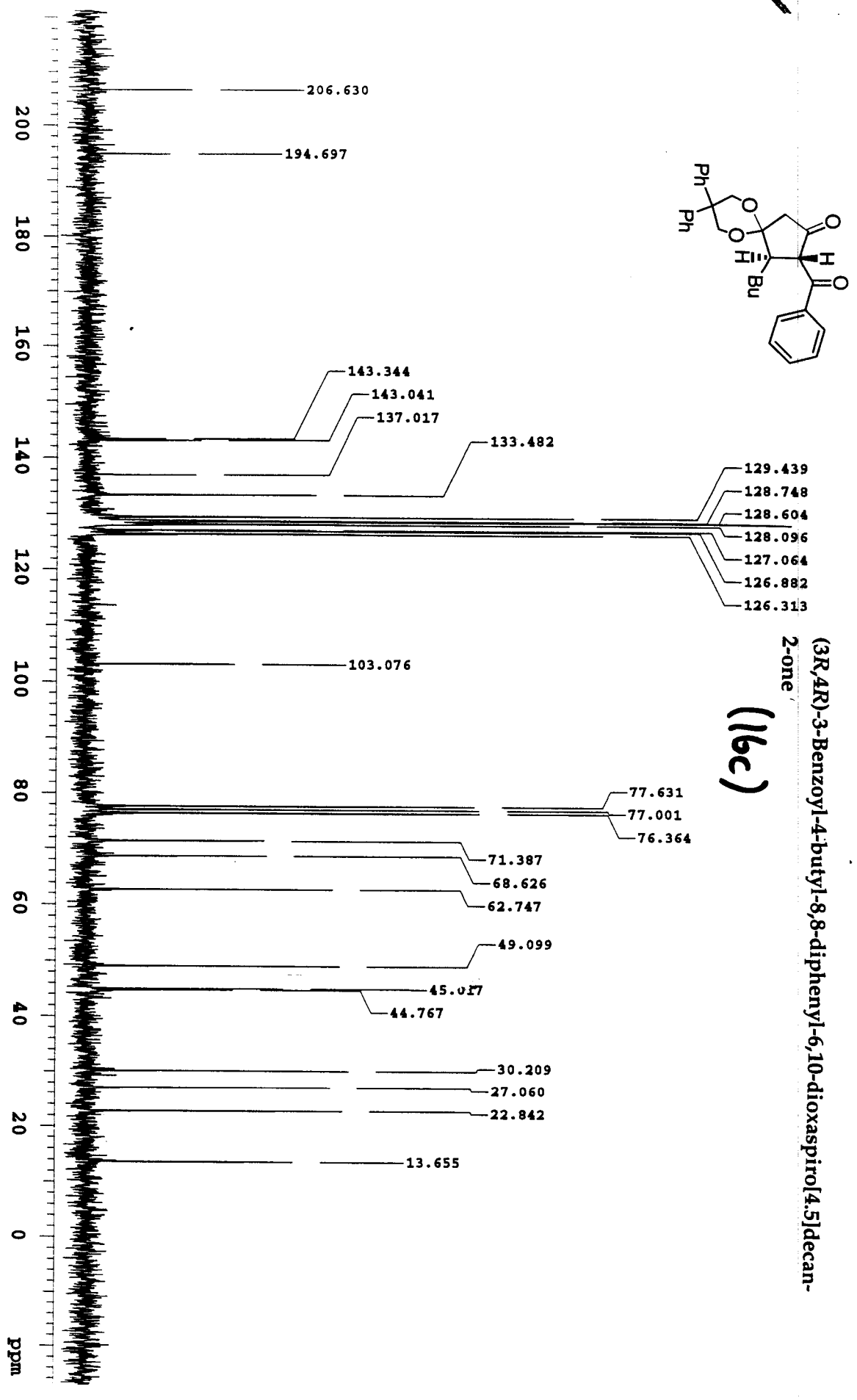
(14c)





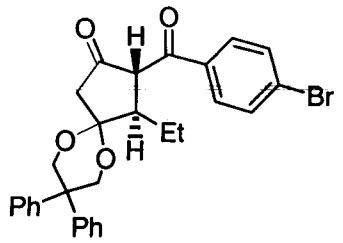
(3R,4R)-3-Benzoyl-4-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one

(15c)



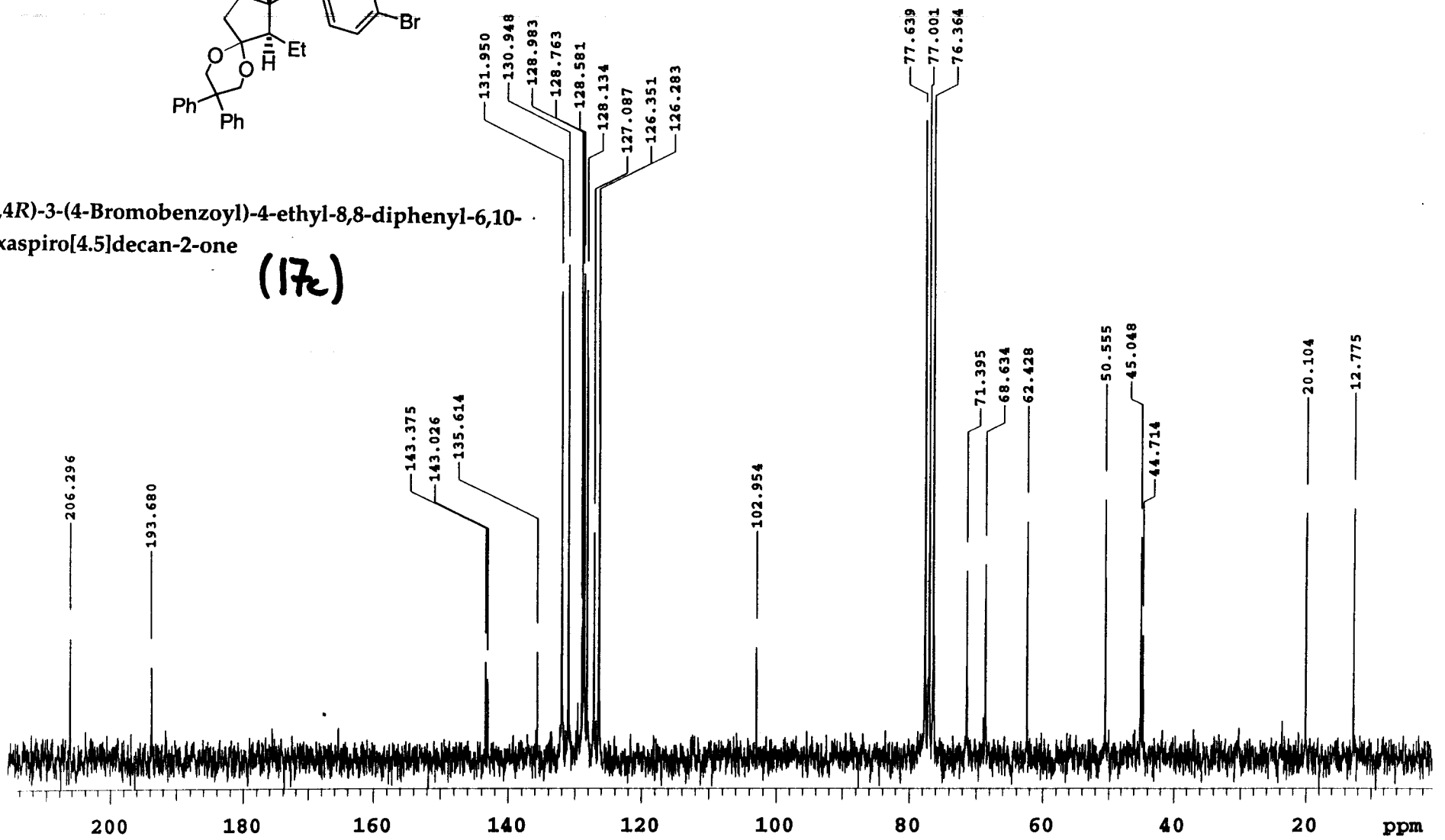
(3*R*,4*R*)-3-Benzoyl-4-butyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one

(16c)



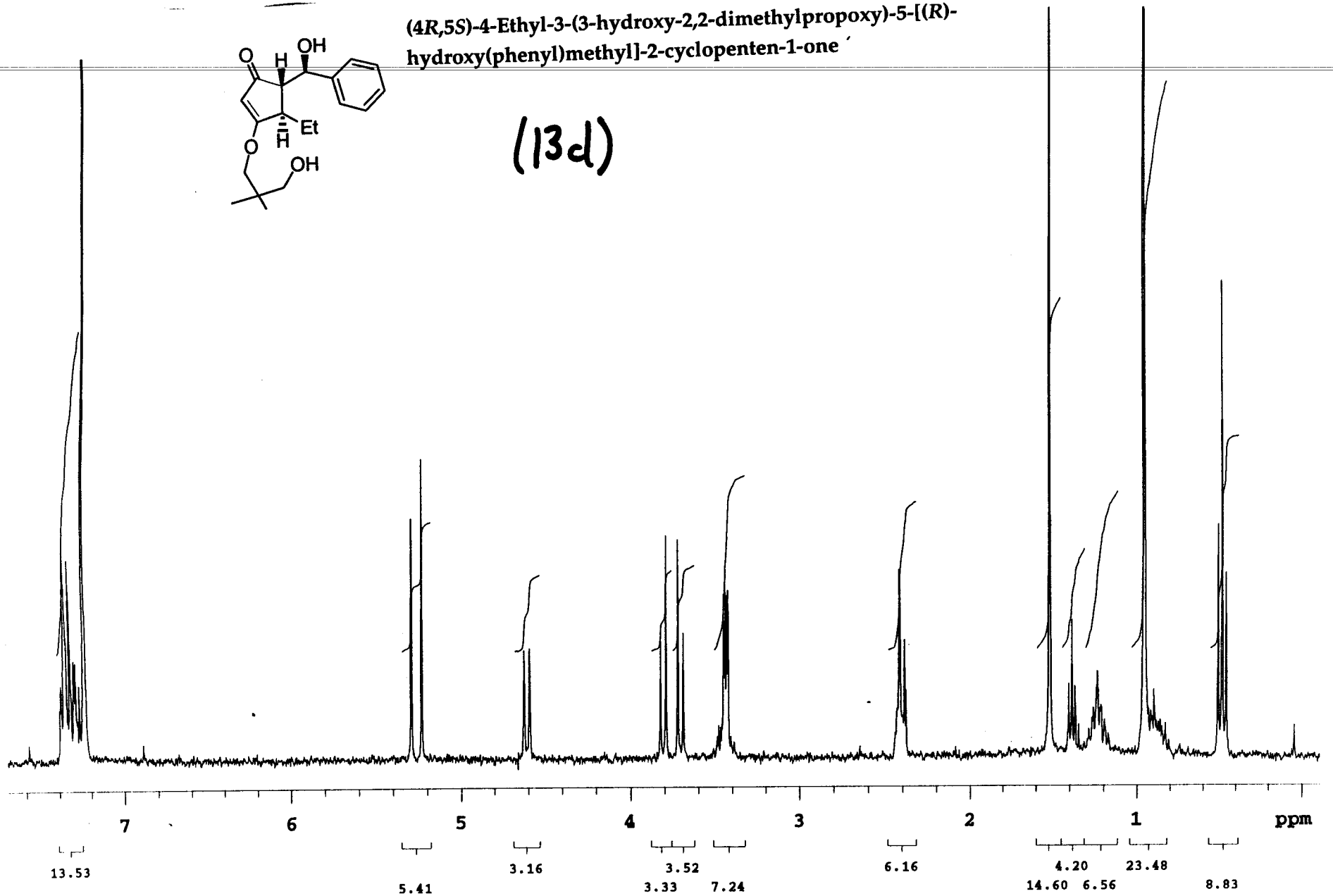
(3*R*,4*R*)-3-(4-Bromobenzoyl)-4-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one

(17c)

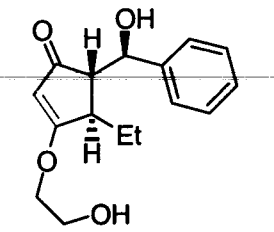


(4*R*,5*S*)-4-Ethyl-3-(3-hydroxy-2,2-dimethylpropoxy)-5-[(*R*)-hydroxy(phenyl)methyl]-2-cyclopenten-1-one

(13d)

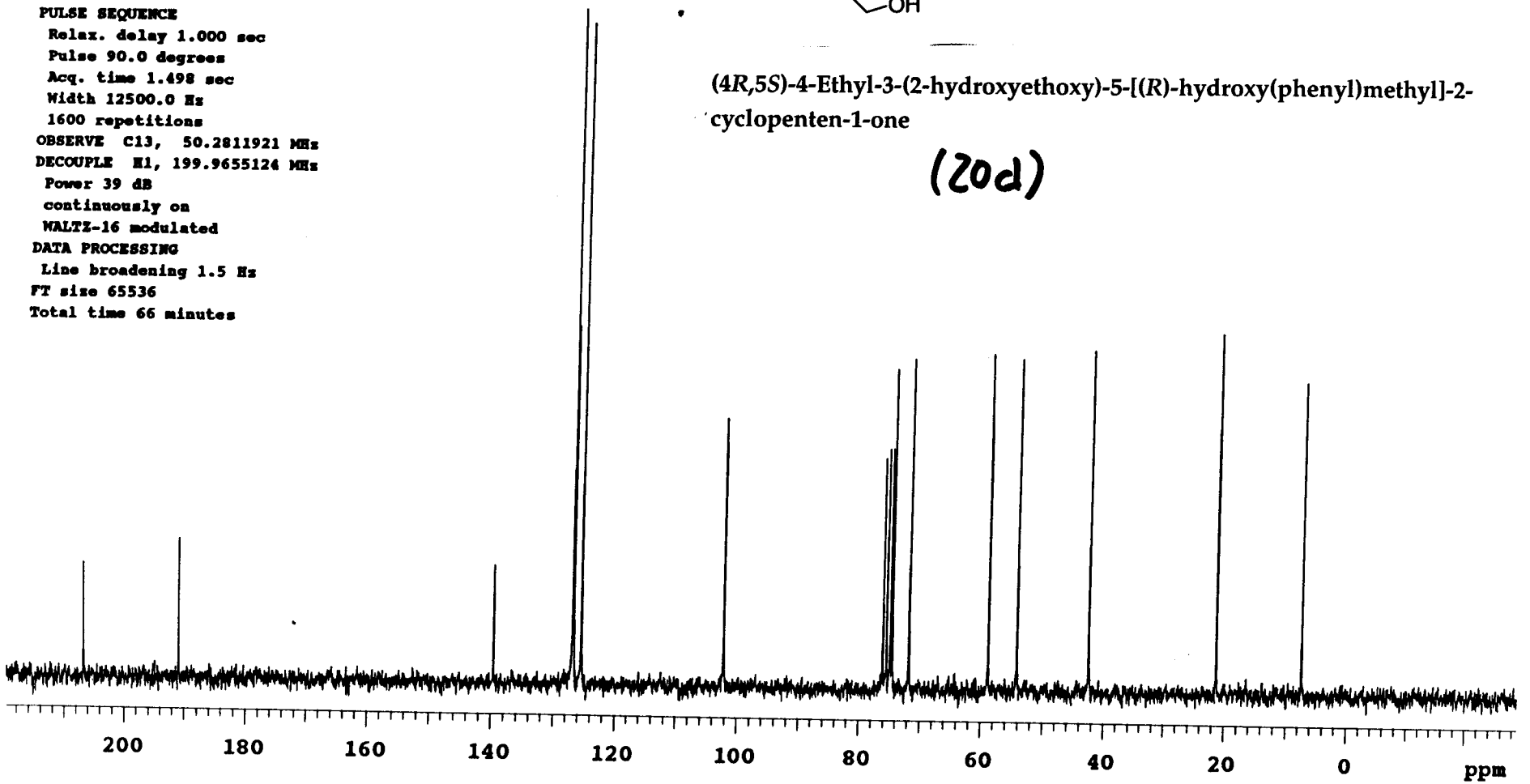


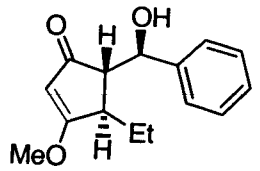
/export/home/vnmr1/vnmrsys/data/auto/tu/0201
Solvent: CDCL3
Ambient temperature
Sample #2
File: 201
GEMINI-200BB "nmr200"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 1.498 sec
Width 12500.0 Hz
1600 repetitions
OBSERVE C13, 50.2811921 MHz
DECOUPLE H1, 199.9655124 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.5 Hz
FT size 65536
Total time 66 minutes



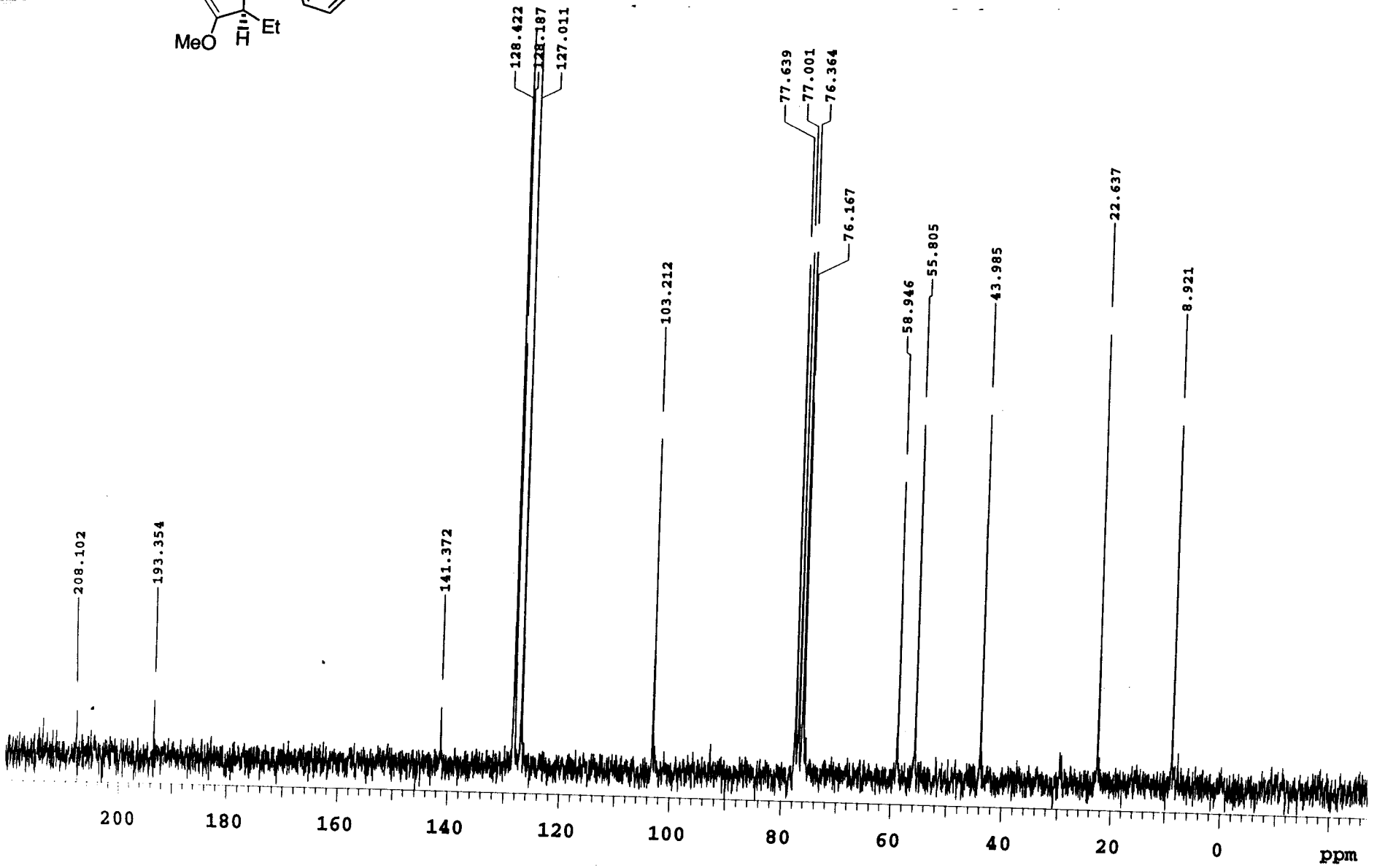
(4*R*,5*S*)-4-Ethyl-3-(2-hydroxyethoxy)-5-[(*R*)-hydroxy(phenyl)methyl]-2-cyclopenten-1-one

(20d)



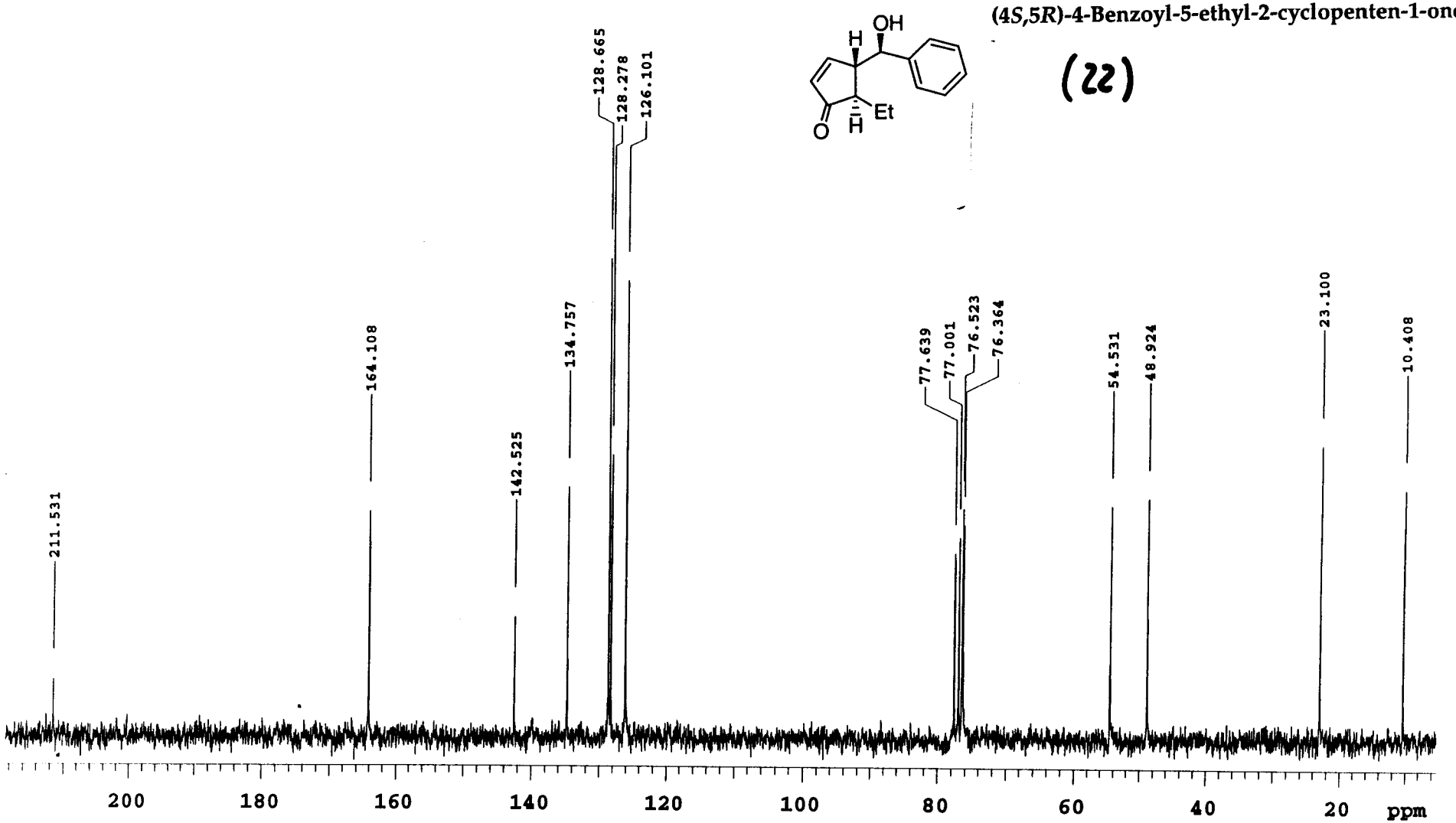


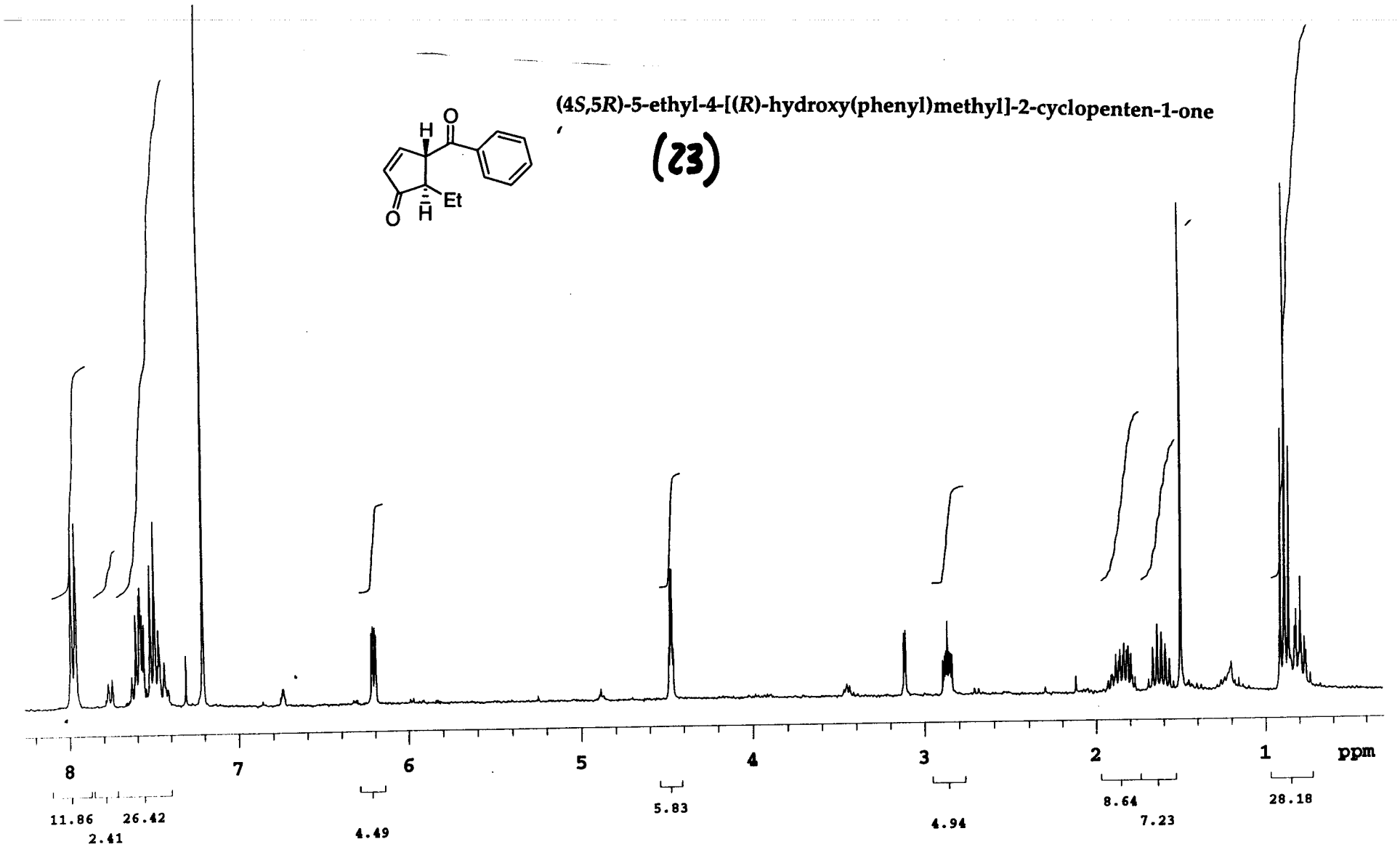
(4*R*,5*S*)-4-Ethyl-5-[(*R*)-hydroxy(phenyl)methyl]-3-methoxy-2-cyclopenten-1-one (21d)



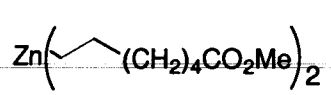
(4*S*,5*R*)-4-Benzoyl-5-ethyl-2-cyclopenten-1-one

(22)

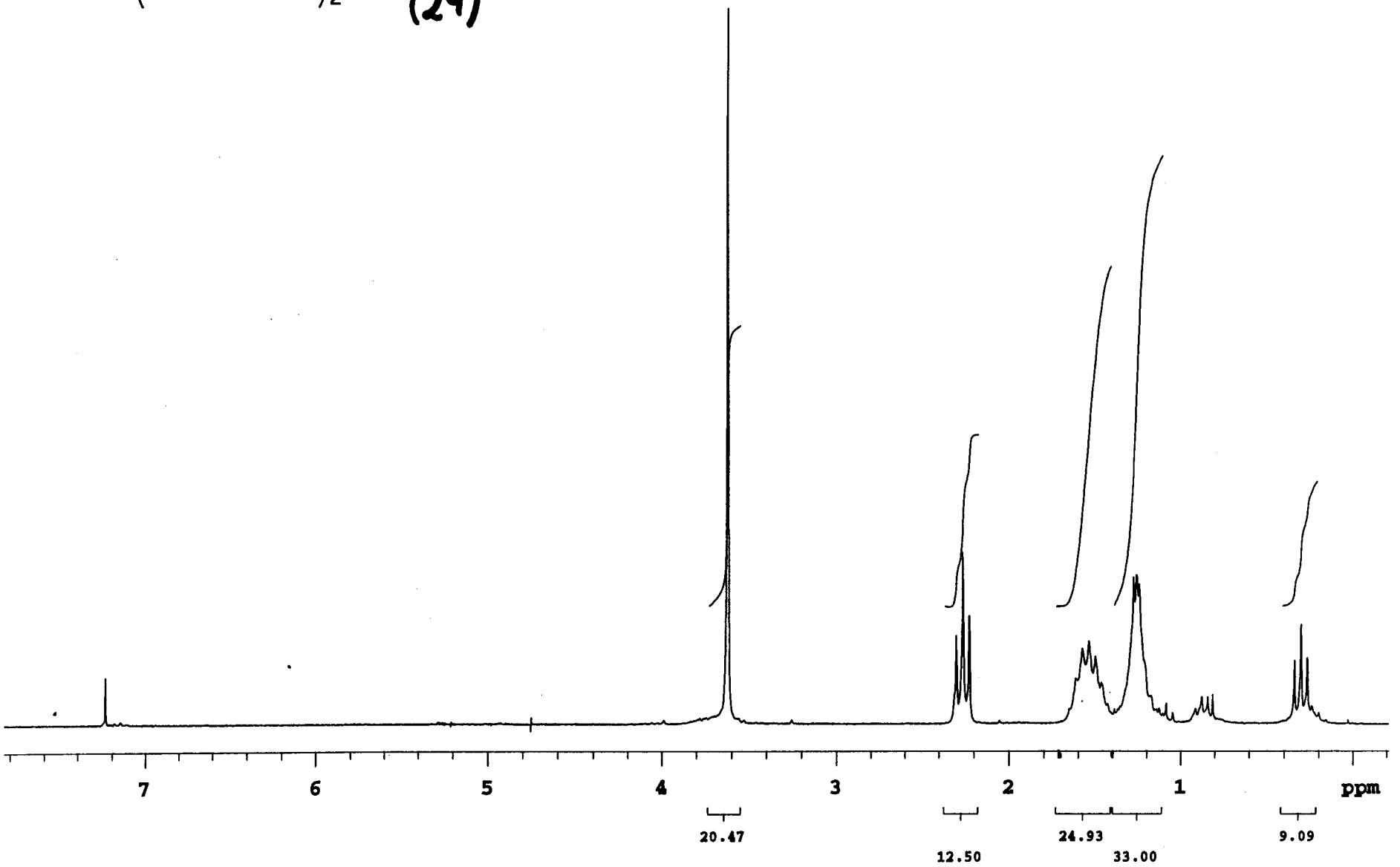


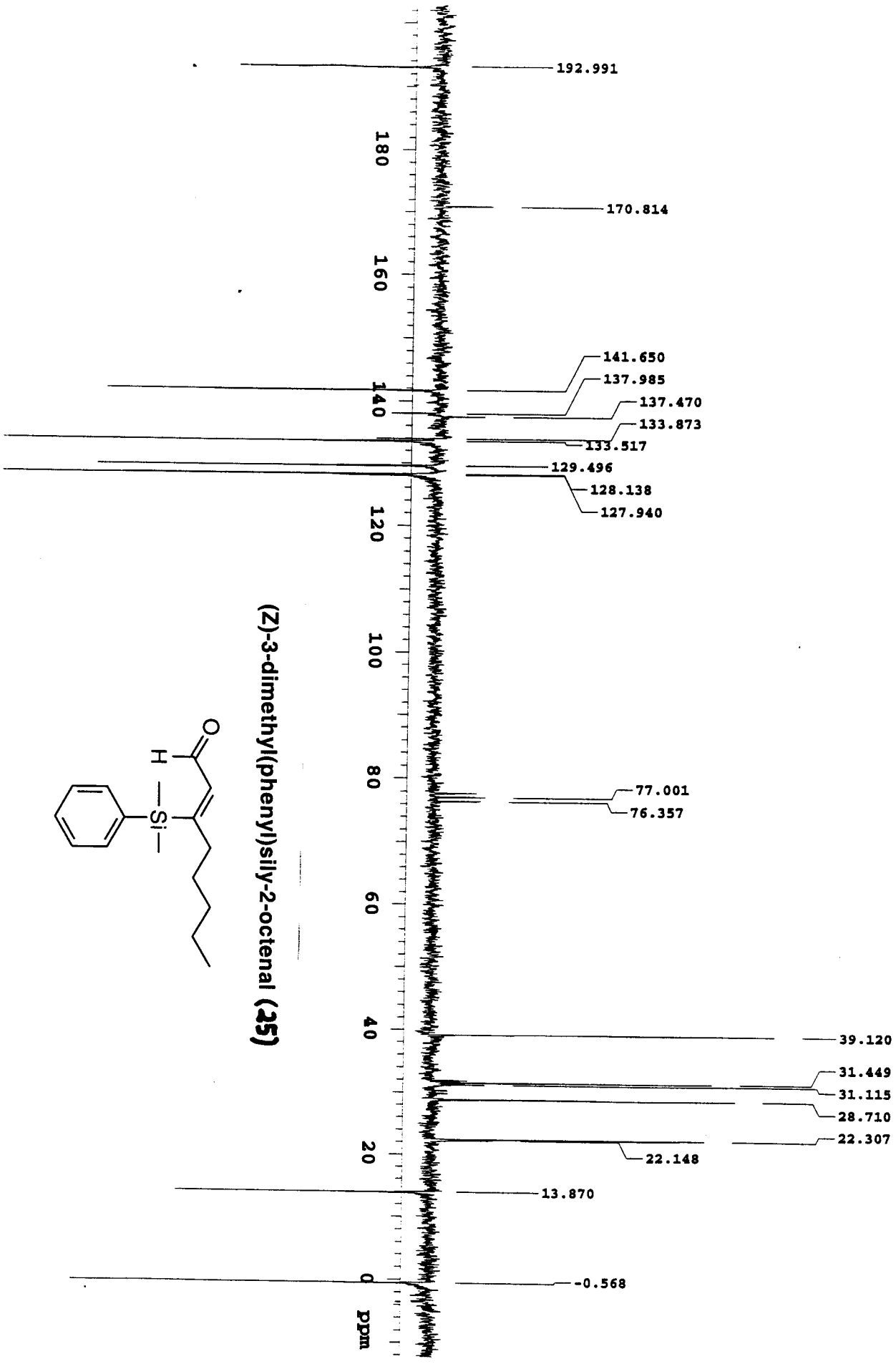

(4S,5R)-5-ethyl-4-[(R)-hydroxy(phenyl)methyl]-2-cyclopenten-1-one
(23)
H
O
Et
O
H
8
7
6
5
4
3
2
1
ppm
11.86
26.42
2.41
4.49
5.83
4.94
8.64
7.23
28.18

Bis(methyl-6-hepanoate)zinc

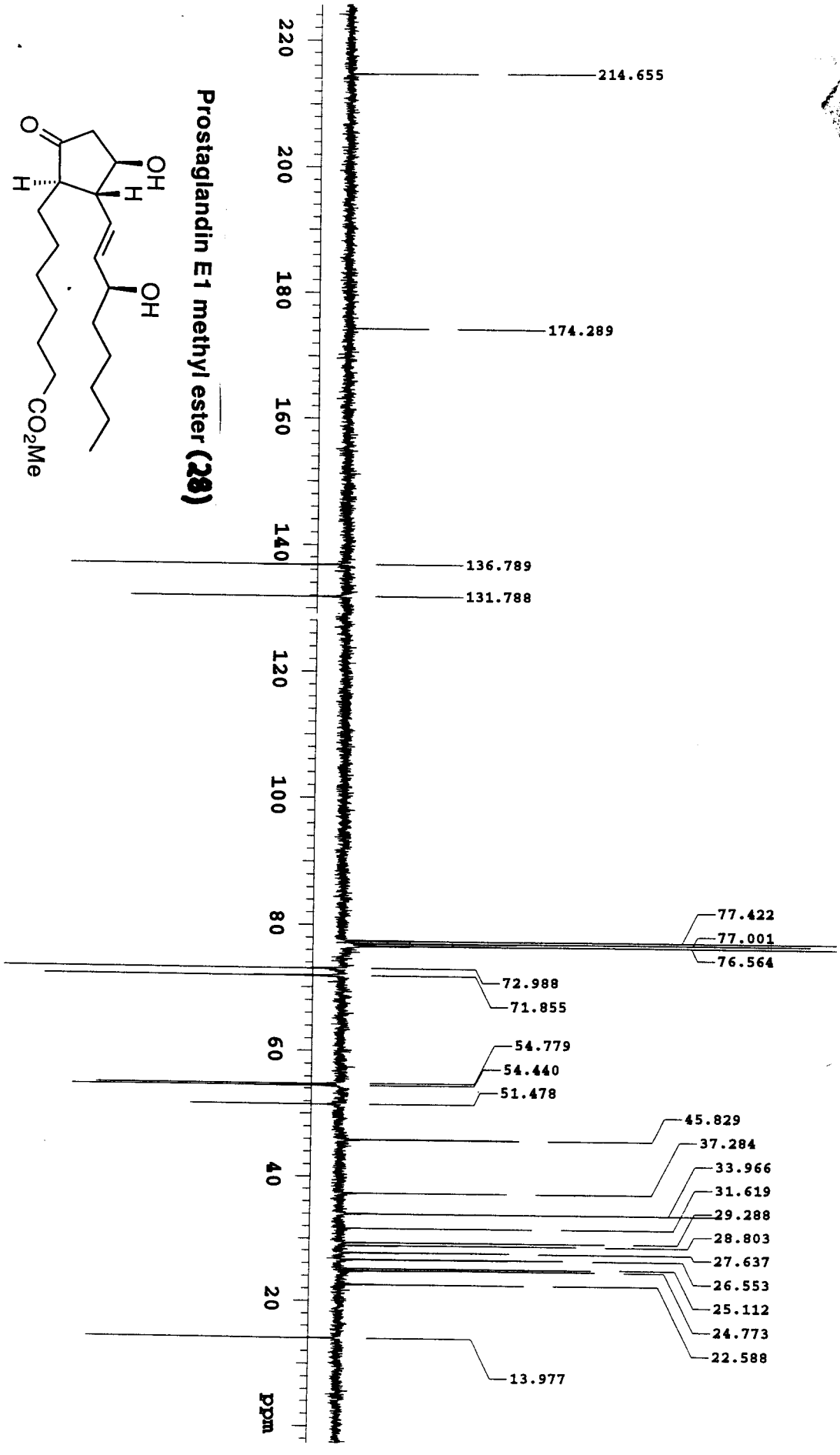


(24)

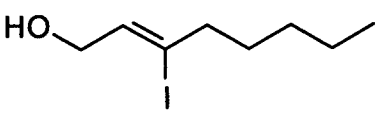


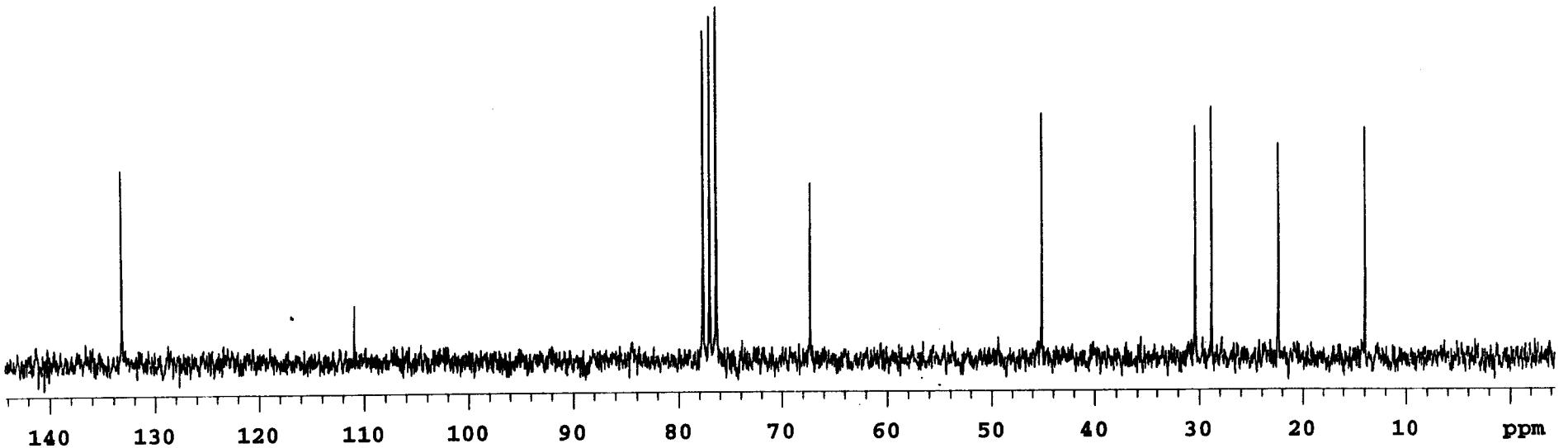


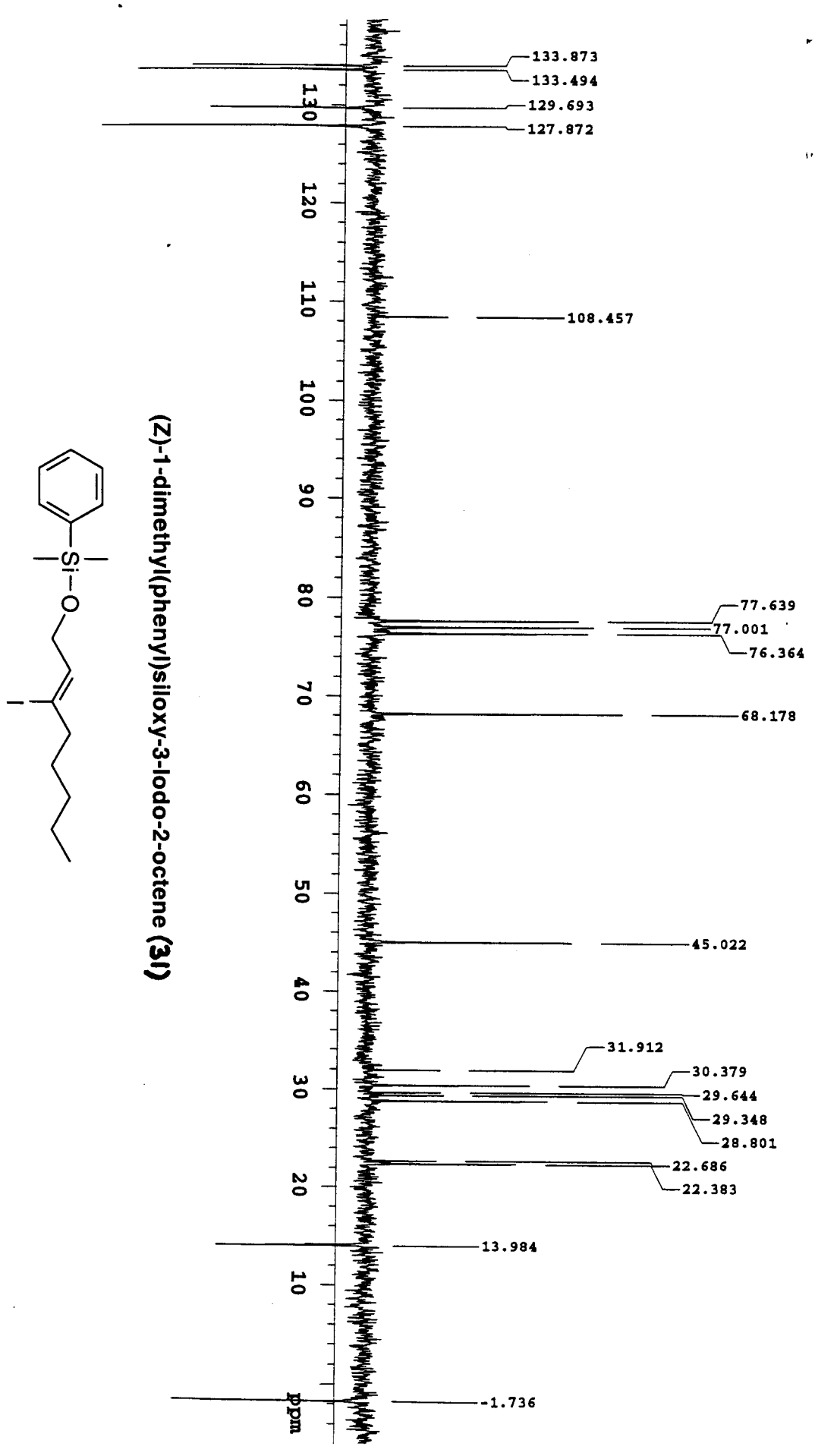
(Z)-3-dimethyl(phenyl)sily-2-octenal (25)

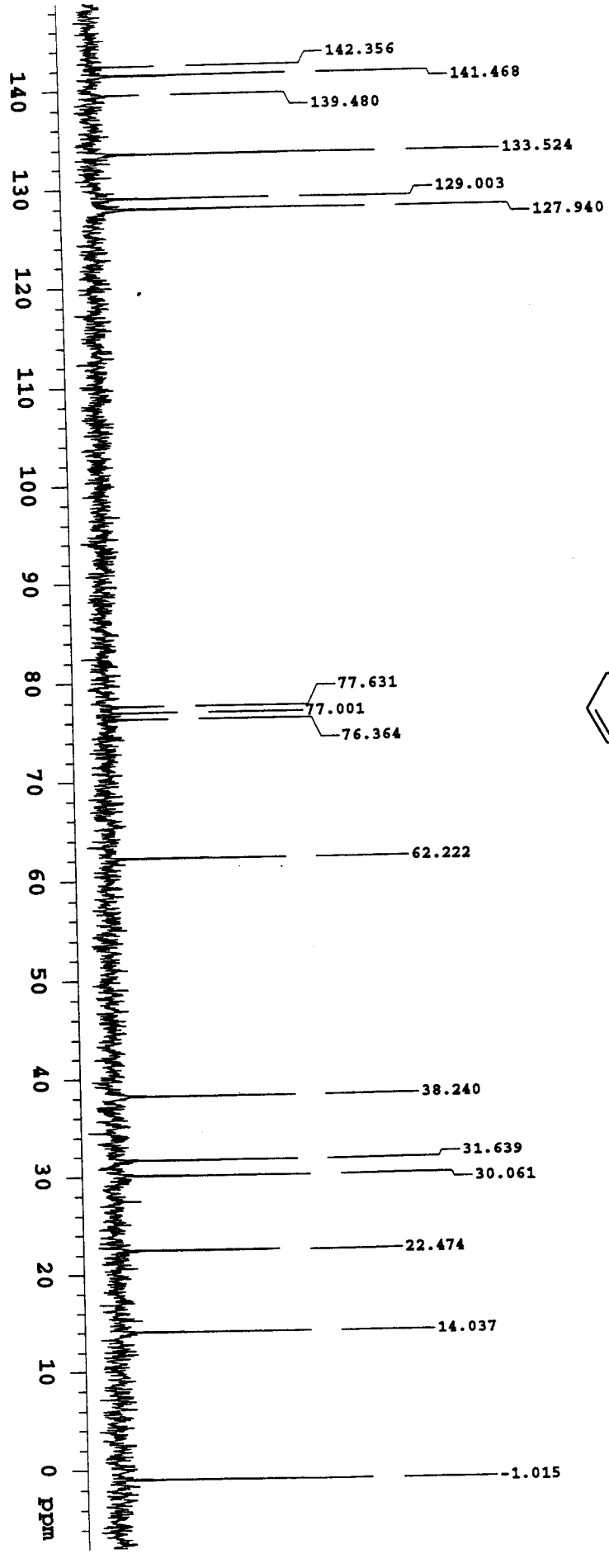

Prostaglandin E1 methyl ester (28)
O
H
OH
H
OH
CO2Me
214.655
174.289
136.789
131.788
77.422
77.001
76.564
72.988
71.855
54.779
54.440
51.478
45.829
37.284
33.966
31.619
29.288
28.803
27.637
26.553
25.112
24.773
22.588
13.977
220
200
180
160
140
120
100
80
60
40
20
ppm

(Z)-3-Iodo-2-octen-1-ol (30)





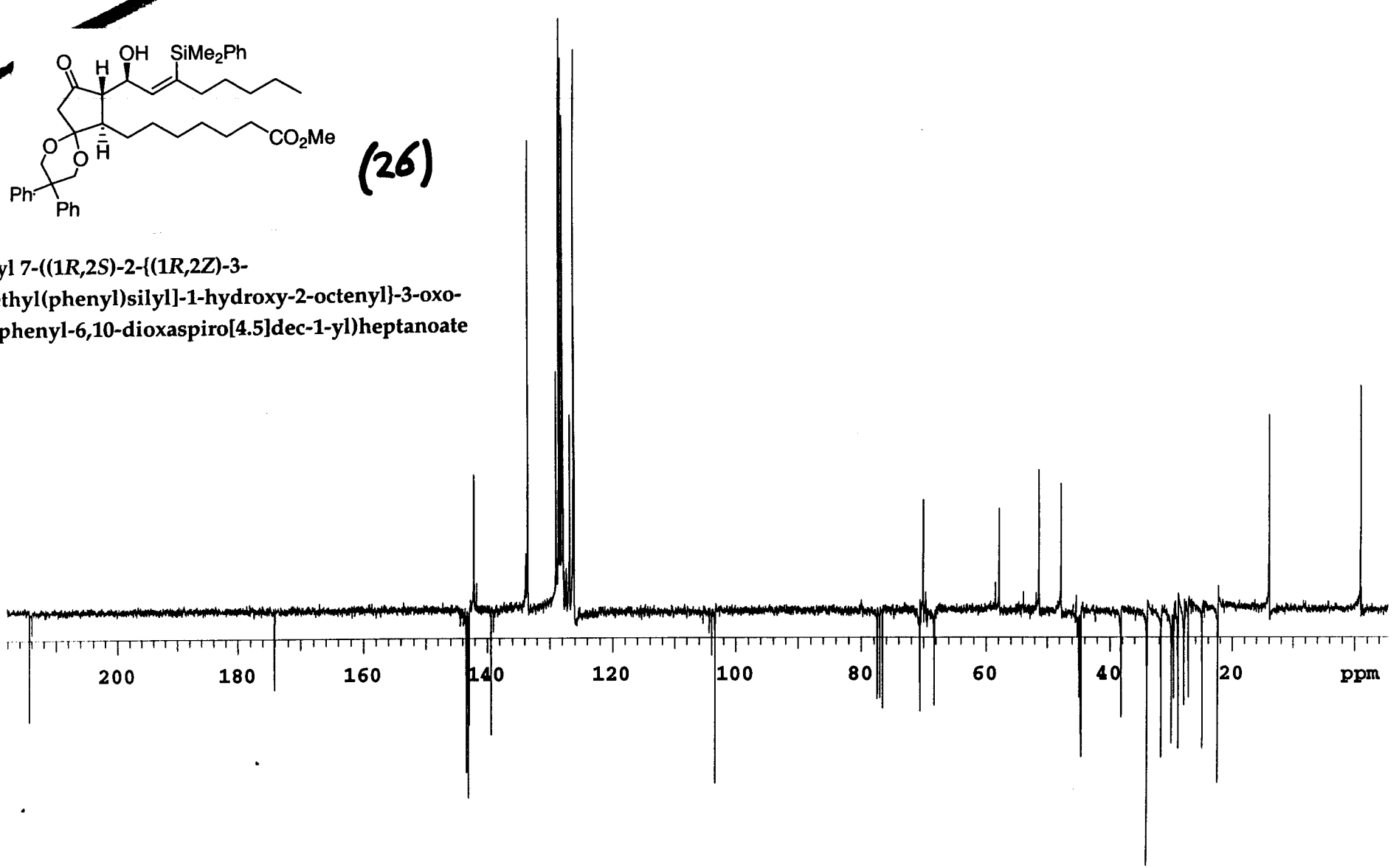

(Z)-1-dimethyl(phenyl)siloxy-3-Iodo-2-octene (3l)
133.873
133.494
129.693
127.872
108.457
77.639
77.001
76.364
68.178
45.022
31.912
30.379
29.644
29.348
28.801
22.686
22.383
13.984
-1.736
ppm

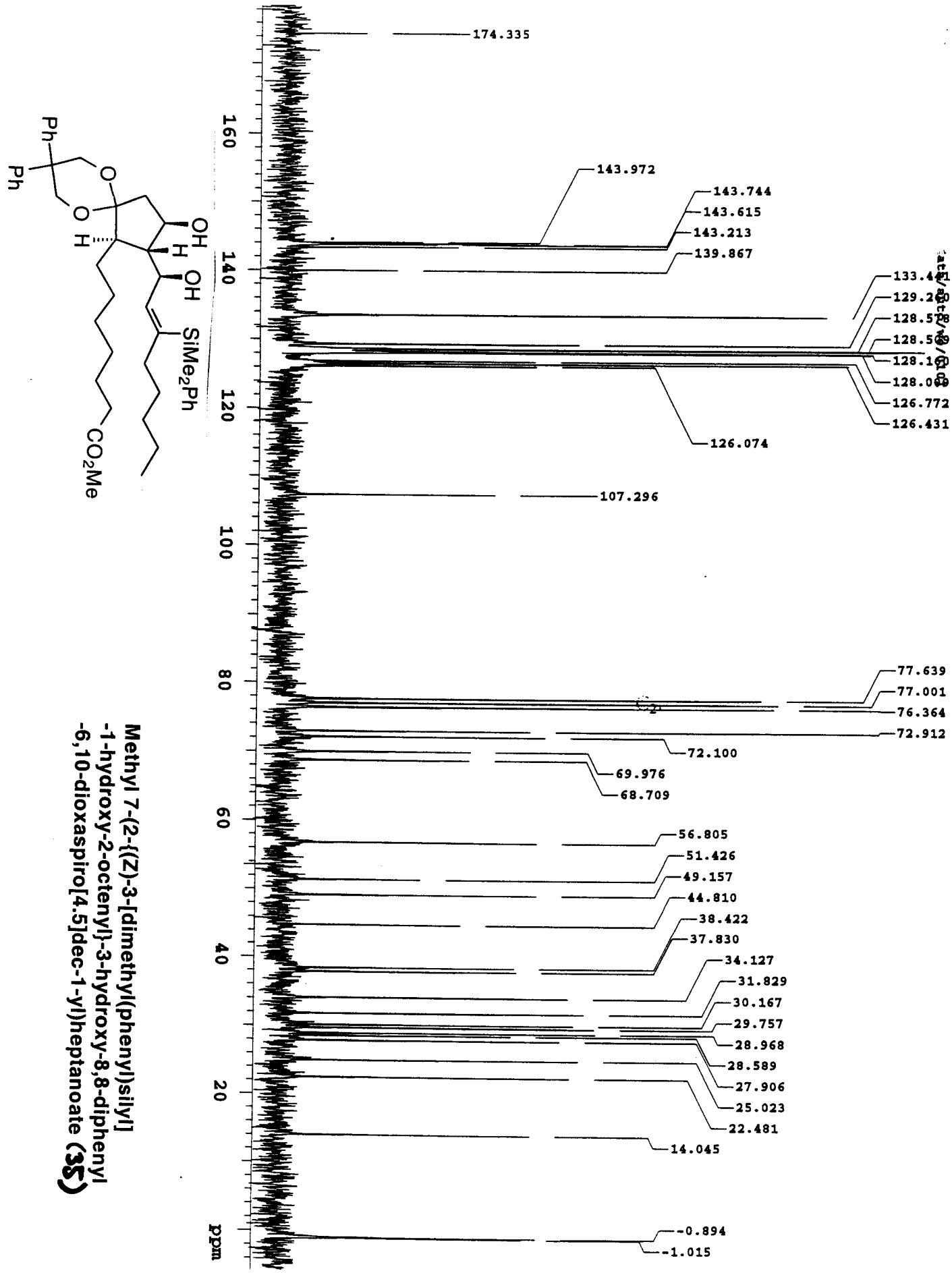


(Z)-3-dimethyl(phenyl)silyl-2-octen-1-ol (32)

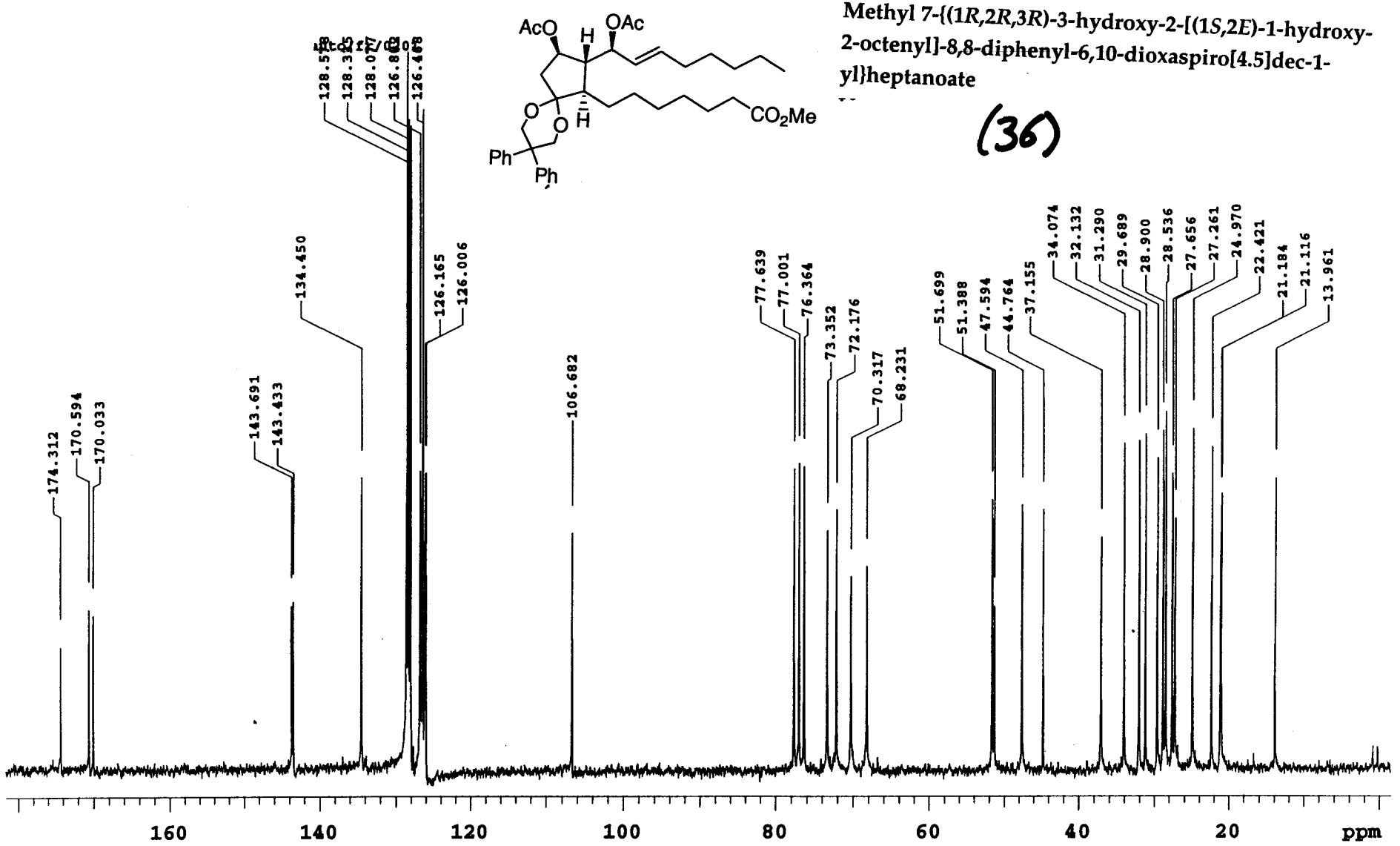
(26)

Methyl 7-((1*R*,2*S*)-2-{(1*R*,2*Z*)-3-[dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl}-3-oxo-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl)heptanoate



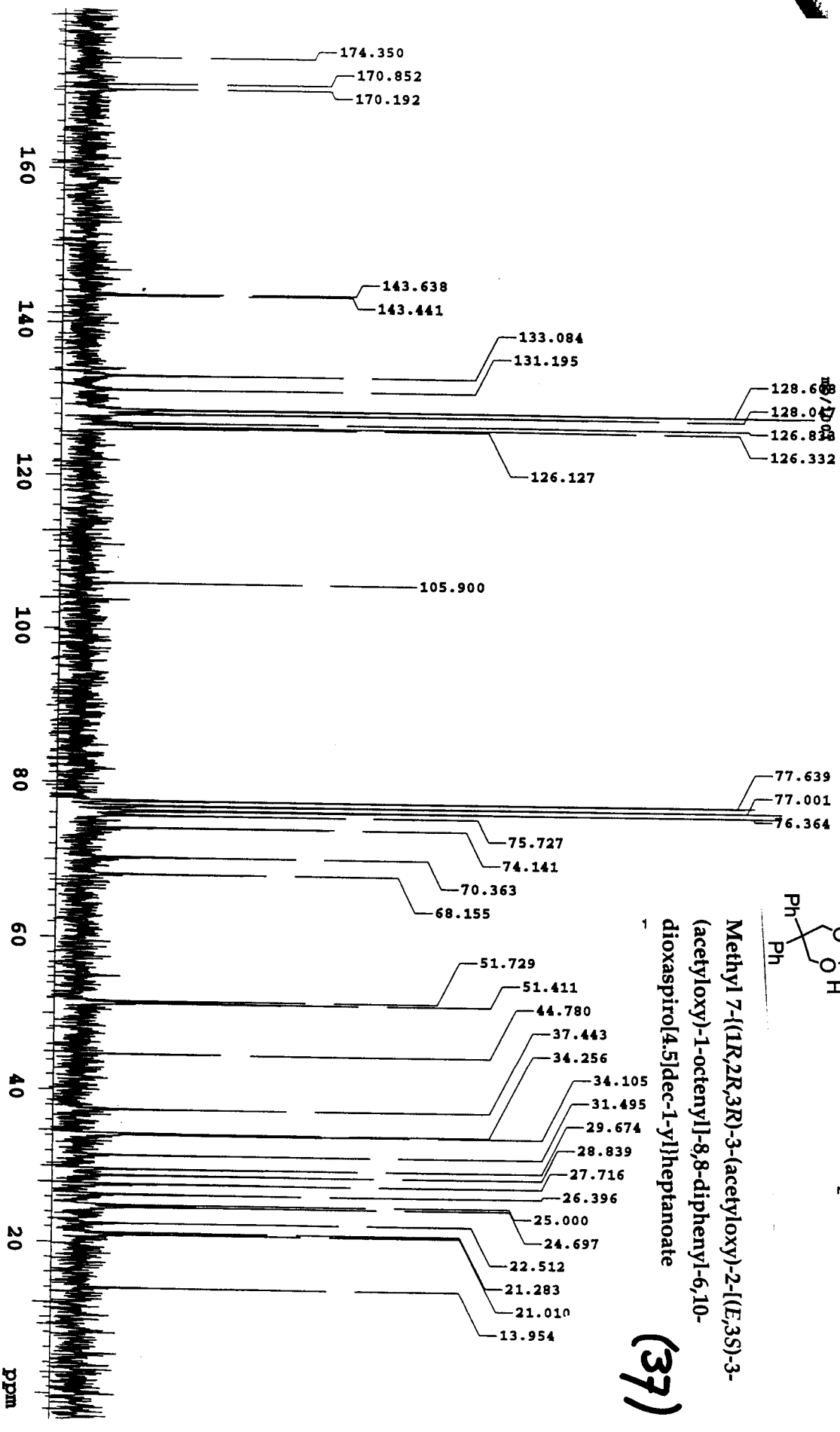


Methyl 7-(2-{(Z)-3-[dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl}-3-hydroxy-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl)heptanoate (35)



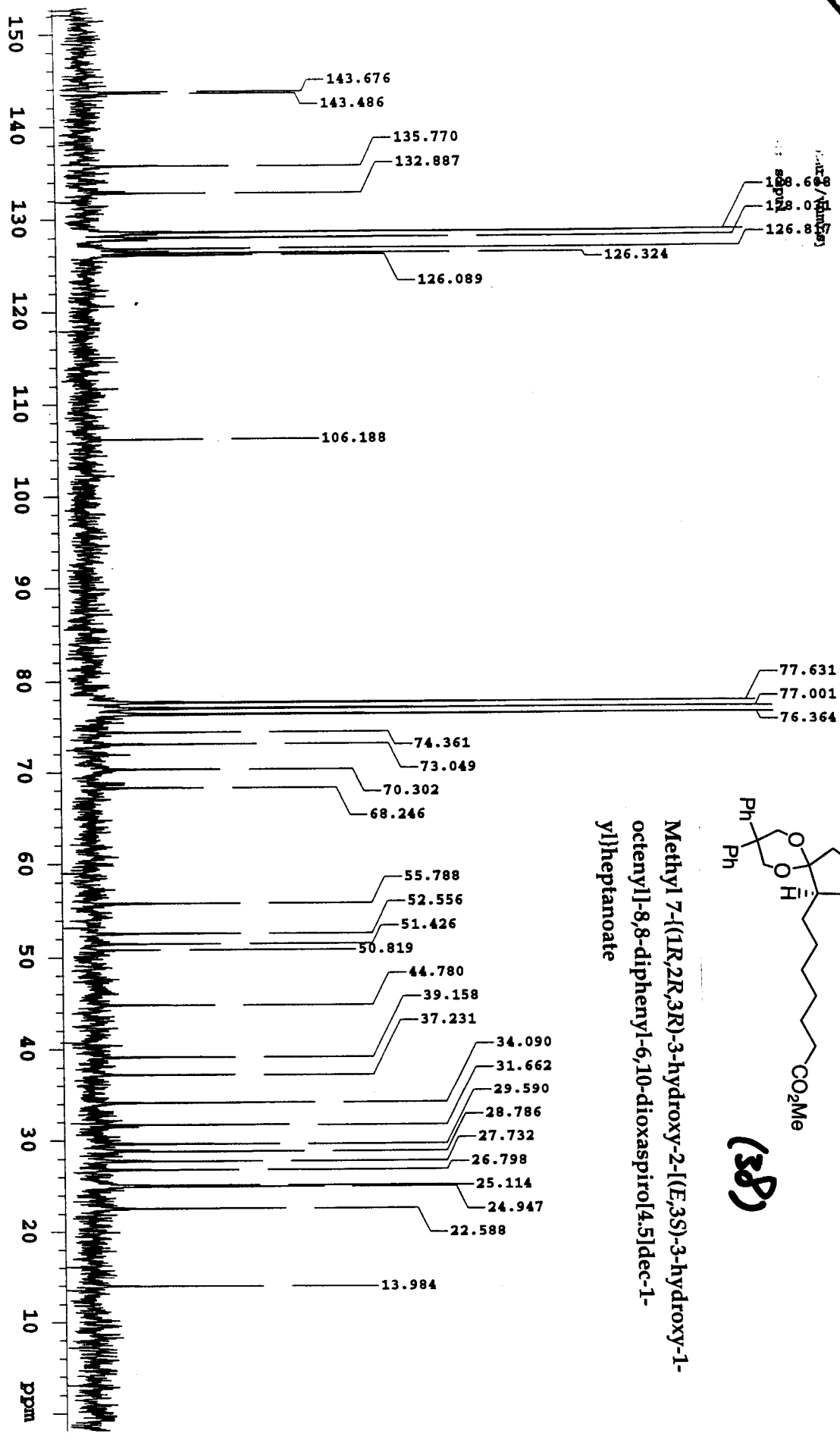
Methyl 7-{(1*R*,2*R*,3*R*)-3-hydroxy-2-[(1*S*,2*E*)-1-hydroxy-2-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl}heptanoate

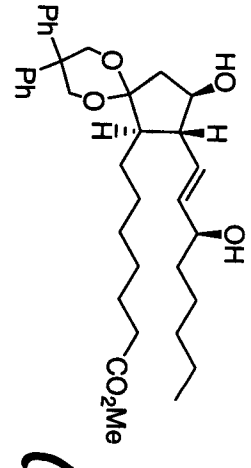
(36)



Methyl 7-{(1*R*,2*R*,3*R*)-3-(acetyloxy)-2-[(*E*,3*S*)-3-(acetyloxy)-1-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl}heptanoate

(37)





(3d)

Methyl 7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*,3*S*)-3-hydroxy-1-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl]heptanoate